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CHLORPROMAZINE AND ENDOCRINE FUNCTION

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Chlorpromazine [Thorazine, largactil, megaphen, 4560 RP, 2-chloro-10(dimethylamino propyl)-phenothiazine] is an extremely interesting drug with regard to its effect on endocrine function. The observation of its hypothermic and hypometabolic effects in 1951 by Laborit and Huguenard (163) was the first stimulus that attracted the interest of endocrinologists to investigate its effects on endocrine activity together with its effect on metabolism and autonomic nervous activity under conditions of temperature changes and other types of "stress." The development of the drug as a tranquilizer and its subsequent widespread clinical use led to the discovery of side-effects such as galactorrhea and amenorrhea. These aroused the interest of many clinicians in its effects on endocrine function. The influence of chlorpromazine (CPZ) and other phenothiazines on the activity of the endocrine glands controlled by the pituitary is a subject of importance for the understanding of the action of these drugs on the central nervous system, and, more generally, of the mechanism of the central nervous control of pituitary function. This review was written to explore these matters.

Chlorpromazine originated in France as a result of studies on phenothiazine an-

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tihistaminics (Phenergan). The classical experiments of Courvoisier *et al.* (71) revealed its manifold actions in animals. Its most important effect apart from its central influences are its adrenergic blocking action together with weak antihistaminic, anticholinergic and antispasmodic effects. It potentiates the effect of hypnotics, alcohol, general anesthetics, local anesthetics and analgesics and it blocks the antiemetic action of apomorphine. Courvoisier *et al.* (71) further found local anesthetic, ganglion blocking and hypotensive effects in addition to diminished capillary permeability, inhibition of clotting of blood and potentiation of the effect of neuromuscular blocking drugs. Hypothermic, antipyretic and anticonvulsive actions are other important features of CPZ. Many aspects of behavior have been studied under its influence (305, 306). It depresses conditioned avoidance behavior, inhibits spontaneous motor activity, decreases agressiveness and hostility, and in higher doses interferes with locomotor function (71, 191, 270, 305, 306). In man it may cause drowsiness and sedation in moderate doses and in larger amounts it causes ataxia and somnolence. For the treatment of mental disorders relatively high doses of CPZ are used ranging from 30 to 1200 mg per day (14).

I. CHLORPROMAZINE AND THE ADENOHYPOPHYSIS

A. Pituitary-gonad axis

In one of the first papers on the effect of CPZ on pituitary-gonadal relationships, Courvoisier and Ducrot (70) reported lack of effect of relatively low doses (1 to 5 mg per kg) upon growth and sexual maturation in the young rat or upon ovulation, fertilization or lactation in the mature female. However, in various species numerous investigators have now shown that CPZ can delay sexual maturation, block ovulation, reduce the weight of ovaries, uteri and vaginae, inhibit ovarian hypertrophy, induce pseudopregnancy, initiate and maintain lactation, cause infertility and abortion, increase the length of gestation, delay nidation, and increase the rate of mortality among the offspring. In the male, atrophy of the sexual organs and a depression of sexual behavior has been found.

These effects suggest that CPZ blocks the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and simultaneously stimulates the secretion of prolactin.

Blockade of the release of FSH and LH is shown by a delay in sexual maturation, failure of ovulation, and atrophy of the ovary, uterus and vagina. Delay in sexual maturation occurs when immature animals are treated for some time with CPZ. Jarrett (133) found a delayed onset of sexual maturity in immature mice with 5 mg of CPZ per kg administered daily. Nagata (203) reported that 2.5 and 5 mg of CPZ per kg for 30 days retarded gonadal development in the female rat. Barraclough and Sawyer (18) found that CPZ in a dose of 5 mg per kg blocks ovulation when injected 3 to 4 hours before the "critical period," which starts at 2:00 P.M. on the day of proestrus under the lighting schedule maintained by these investigators. CPZ also prevents the superovulation produced by a single injection of pregnant mare serum gonadotrophin in immature rats (302). Since

extracts of bovine median eminence elicited ovulation in animals so treated, we can deduce that the site of action of the drug is in the central nervous system.

Although various authors failed to find gonadal atrophy in rats after CPZ in doses between 1 and 40 mg per kg administered for various periods of time (12, 35, 70, 71, 183), Sulman (271) showed that treatment of female rats for 3½ months with 10 mg of CPZ per kg reduced ovarian weight. The number of corpora lutea in the ovaries was low. Ovarian atrophy was also observed by Reiss (237) and Benson (23). Gitsch (111) showed that hypertrophy of implants of ovaries and uteri in the spleen of castrated rats was prevented by daily doses of 10 mg of CPZ per kg. The inhibited ovarian growth and histological characteristics of the implants suggested that FSH release was blocked. Inhibition of myometrial hypertrophy of implanted uteri suggested estrogen deficiency; this could result from lack of FSH. Jarrett (133) observed that the ovarian hypertrophy that follows removal of one ovary in mice was inhibited by 10 daily treatments with 10 mg of CPZ per kg. Histological changes in vaginae and uteri of CPZ-treated mice were consistent with estrogen deficiency. This author also found CPZ to increase the amount of gonadotrophin in the pituitary. Khan and Bernstorf (144) showed that compensatory ovarian hypertrophy in prepuberal rats was inhibited by daily treatment with 10 mg of CPZ per kg for 33 days. The fact that the remaining ovaries were small and immature indicates lack of secretion of gonadotrophins.

The findings cited suggest that CPZ inhibits activity of gonadotrophic hormones. This effect might be the result of blockade either of the release of these hormones from the anterior pituitary or of their direct action on the target glands. In fact, evidence has been obtained that the blocking action of CPZ is exerted on the gonads by inhibition of the effect of gonadotrophins especially when large doses of phenothiazines are used (302). Purshottam *et al.* (232) found that CPZ (about 10 to 25 mg per kg) inhibits ovulation in mice on a regimen of pregnant mare serum gonadotrophin and human chorionic gonadotrophin that normally results in superovulation. Another phenothiazine, perphenazine, (Trilafon), had the same effect with lower doses. Still another phenothiazine, promethazine, depresses the effect of gonadotrophic hormone on the prostate and vesicula seminalis of the rat (183). A similar effect was found with 6 mg of CPZ per day for 3 days on the vesicula seminalis of the rat treated with 2 IU of human chorionic gonadotrophin (35). Dasgupta and Häusler (80) observed that it did not interfere with estrus induced with estrogen in ovariectomized rats. Lewin *et al.* (169) also did not find an inhibitory effect of CPZ in castrated rats treated with estrone. In mice made noncyclic by treatment with CPZ, Cranston and Segal (74) found that the administration of pregnant mare serum gonadotrophin induced estrus in all animals. Simultaneous administration of 10 IU of pregnant mare serum gonadotrophin and 20 IU of human chorionic gonadotrophin daily prevented ovarian atrophy in rats treated for 3½ months with 10 mg of CPZ per kg (271). In addition Chatterjee (52) showed that the administration of 15 mg of CPZ per kg daily for 15 days, which induced pseudopregnancy, did not interfere with an increase in folliculogenesis, estrous vaginal smears, or in-

creased uterine weight induced by pregnant mare serum gonadotrophin. In contrast, rabbits treated with 5, 10 or 20 mg of CPZ 1 hour before and 5 and 11 hours after 10 IU of chorionic gonadotrophin failed to ovulate (275).

CPZ seems to interfere with the effect of gonadotrophins on the gonads only in high doses, but even these doses do not antagonize the effect of estrogens on the target organs. It is therefore likely that the block of ovulation by CPZ in moderate dosages is due to a decreased secretion of FSH and LH as a result of an inhibitory action on centers in the brain involved in the release of gonadotrophins. Blockade depends on the dose of the drug used and the intensity with which the pituitary is forced to release gonadotrophins. For example, CPZ fed to a strain of mice (C_3H) as 0.2 and 0.3% of the diet led to a decrease in estrous cycles, but it did not inhibit subestrous in ovariectomized mice that secrete estrogens from adrenal estrogen-secreting tumors. These tumors secrete in response to gonadotrophin. Thus, whereas CPZ reduced the secretion of gonadotrophins in intact mice, it failed to block the increased release of gonadotrophins in ovariectomized animals (304).

Increased secretion of prolactin coincides with inhibition of FSH-LH release. Initiation or maintenance of milk secretion and mammary growth, persistence of corpora lutea, and the occurrence of pseudopregnancy as indicated by the deciduoma reaction in the uterus, are parameters of an increased prolactin secretion.

The elegant technique of Meites *et al.* (185) with cultured anterior pituitaries, which secrete measurable quantities of prolactin, has been used to explore the effect of drugs on prolactin release. Pasteels (217, 218) and later Meites *et al.* (186) showed that adding extracts or explants of hypothalamus to the cultures decreased the quantity of prolactin released into the medium. Danon *et al.* (78) showed that hypothalamus obtained from rats treated with the phenothiazine derivative, perphenazine, when added to cultures of pituitaries, does not inhibit prolactin secretion. This strongly supports the hypothesis that phenothiazines antagonize the normally operating inhibitory influence of the hypothalamus on the secretion of prolactin. The prolactin-releasing effect of CPZ is also evident from the finding by Assenmacher and Baylé (11) that CPZ administered to immature pigeons leads to a significant thickening of the epithelium of the crop-sac.

In mature animals phenothiazines inhibit the occurrence of estrous cycles. A strain (ZBC) of mice treated for 20 days with CPZ or promazine in the diet had a marked decrease in the number of cycles in doses which did not induce severe loss of body weight. Since food restriction *per se* could not elicit such a high incidence of estrus block, the estrus inhibition cannot be attributed to the reduction in food intake caused by the drug (74). Others also found prolongation of estrous cycles in mice (133) and in rats (144, 159, 169). This may indicate either blockade of ovulation or induction of pseudopregnancy. A decrease in the number of corpora lutea in the cyclic or pregnant rat occurs after treatment with CPZ (2, 48) and the drug antagonizes formation of deciduoma in rabbits (141, 142). However, in rats treated with CPZ, Barraclough (17) found pseudopreg-

nancy, as shown by the occurrence of deciduoma. Barraclough and Sawyer (19) showed that CPZ induces pseudopregnancy in every case when the treatment is begun on day 1 of diestrus, whereas, if CPZ is given during proestrus or estrus, pseudopregnancy occurs in 50 to 60% only. They reasoned that if CPZ is administered too late, regression of corpora lutea might have taken place already and that new corpora lutea had to be formed first before an effect is found. A single injection of 10 mg of CPZ per kg delays the occurrence of subsequent estrous cycles of all rats when injected at day 2 of estrus (144), whereas, if the drug is injected at day 1 or 2 of diestrus, pseudopregnancy is observed in 50 to 60%. No effect is found if CPZ is administered at day 1 of estrus. Accordingly, induction of pseudopregnancy by CPZ seems to depend on the state of corpora lutea present at the moment the treatment is started. The incidence of pseudopregnancy is highest 24 hours after the day the earliest corpora lutea are found, *i.e.*, on the first day of diestrus in animals showing 1 day of estrus and on the second day in animals showing 2 days of vaginal estrus. Khan and Bernstorf (144) also found that the weight of the ovaries of prepuberal castrated rats grafted in the stomach wall were increased by CPZ treatment. Corpora lutea appeared to form the bulk of the graft. This finding again suggests enhancement of prolactin secretion by CPZ. Others also found pseudopregnancy on treatment with phenothiazines (228, 229, 284). Jarrett (133) failed to induce pseudopregnancy in mice. This was thought to be due to species differences since deciduoma formation does not take place in mice as readily as in rats.

CPZ stimulates mammary growth (114). Grönroos *et al.* (114) found that in daily doses of about 15 mg per kg for 7 days it causes multiplication and epithelial proliferation of the mammary ducts of female rats. Hardly any signs of secretory activity were found in the alveoli. Treatment with CPZ causes the same alteration in mammary gland cells as with prolactin (59). Talwalker *et al.* (278) found that CPZ in doses of 5 or 15 mg per kg daily for 5 days caused alveolar growth and milk secretion in virgin rats primed with estradiol. The higher dose also caused maintenance of mammary lobulo-alveolar structure and secretion in postpartum rats for 10 days after removal of the litter. Interestingly, neither prolactin nor adrenocorticotrophic hormone (ACTH) alone could initiate mammary secretion in rats primed with estrogen, as did CPZ, but when they were given in combination they were active. Accordingly, CPZ causes mammary growth and secretion by release of both prolactin and ACTH. Since CPZ does not induce mammary growth in hypophysectomized rats primed with estradiol, the pituitary or the brain would seem to be the site of action of the drug. With 3 mg of CPZ per kg daily in immature rats primed with estradiol, Langer and Gnudi (167) also found tubulo-alveolar hyperplasia and secretion. Benson (23) reported that 2.5 and 5 mg of CPZ administered daily to female lactating rats had a weak retarding effect on mammary involution, and these doses for 9 days did not cause ACTH release from the pituitary as indicated by the absence of adrenal hypertrophy and involution of the thymus. Yokoyama and Sawyer (301) found a well maintained lobulo-alveolar structure in the mammary glands 5 days after weaning in mother rats treated with 5 or 10 mg of CPZ daily during the 5 last days of suck-

ling. In a comparative study on the mammatropic effect of various phenothiazine derivatives injected for 7 days in female rats, using microscopic examination of the left inguinal mamma to determine the effect of the drugs, Khazan *et al.* (146) found that CPZ was among the most active of the phenothiazines capable of inducing secretory activity in the mammary gland. Finally, Mishinsky *et al.* (193) showed that implantation of perphenazine crystals at the end of steel tubes in the median eminence of rabbits caused a marked mammary development and copious milk production. Accordingly, there exists abundant evidence in the literature that CPZ causes the release of prolactin.

A number of observations may be best explained by interference of CPZ with release of gonadotrophic hormone or by other effects of the drug. Delayed implantation of the ova in the uterus has been observed after treatment with CPZ. A dose of 0.1 μg of estradiol injected on days 3 and 4 of pregnancy in rats prevents the delay in nidation due to CPZ (228, 230). Psychoyos (231) suggested that the cause of the delay is a deficiency in estrogen. This is in agreement with findings of Whitten (297) and Bloch (27). However, Chambon (50) obtained a normal nidation in CPZ-treated rats by daily injection of progesterone or prolactin. Since CPZ induces the secretion of prolactin and the subsequent production of progesterone, it is difficult to interpret this finding. Delayed nidation also occurs during lactation (68) and in rats bearing autografted pituitaries (91) or with electrolytic lesions in the median eminence (102). Since in all these circumstances prolactin release is stimulated, but the release of FSH-LH is impaired, it is inferred that delayed nidation is due to estrogen deficiency.

Chronic treatment of pregnant mice with CPZ by mouth in doses of 4 and 16 mg per kg leads to a significantly lower number of offspring, while mean litter weights are lower (212). The drug apparently interferes with fertilization and postconception implantation. In rats treated during pregnancy, Ordy *et al.* (212) and others found longer gestation, higher fetal mortality rate, underdevelopment of the offspring, and more frequent abortions (48, 49, 202, 240). In contrast, 10 mg of CPZ per kg daily administered to rats during pregnancy and lactation failed to affect duration of pregnancy, and the offspring were indistinguishable from those of control mothers (159). Similarly, Courrier and Marois (69) failed to affect pregnancy in rats by treatment with 10 mg of CPZ per kg given between the eighth and sixteenth day's of gestation. However, Chambon (47) reported that 10 mg of CPZ per kg every 8 hours for 3 days induced abortions, especially in the early stage. The number of abortions was largest when the drug was given during the sixth to tenth days of gestation and smaller when administered between days 9 and 12, and none were induced when CPZ was injected after the twelfth day. Accordingly, a rather high dose of the drug seems to be necessary during a critical period in order to produce abortion.

Not much work has been done on the effect of CPZ on gonadal function in the male. A dose of 2.5 mg per kg daily for 4 weeks did not affect the weight of the male gonads (183). Sulman (271) found that 10 mg of CPZ per kg daily in long-term experiments caused testicular atrophy. Male rats treated for 30 days every second day with 25 mg of CPZ per kg had atrophied testes and seminal vesicles,

which upon histological verification were indistinguishable from those found in hypophysectomized rats (53). The author concluded that CPZ blocks release of gonadotrophin in the male rat. However, CPZ in doses between 1.5 and 6 mg per day for 3 days to male rats, inhibits the effect of gonadotrophins on vesiculae seminales (35). This was also found with promazine (183). Nagata (203) reported that 5 mg of CPZ per kg daily for 30 days retarded while 2.5 mg per kg stimulated gonadal development in the male rat. Zimbardo and Barry (303) and Gillet (110) found a reduction in the copulation rate but not the percentage of rats that would copulate. In contrast, Foote and Gray (98) failed to observe a reduction in libido of dogs trained to routine semen collection. The motility of sperm was unaffected and sperm production was even higher than normal. The amount of CPZ (4.4 mg per kg) used was rather low. CPZ added in moderate doses to bull sperm *in vitro* failed to affect motility and fertility (97) although levels above 0.2 mg per ml were spermicidal.

B. Pituitary-thyroid axis

Conclusions drawn from experiments on the effect of CPZ on thyroid function vary considerably. This is caused by the various measures used to determine thyroid activity, the different dosages and the duration of the treatment employed, and differences in experimental circumstances, especially with regard to environmental temperature. Using ^{131}I-uptake by the thyroid as a measure of pituitary-thyroid activity, several workers observed a decrease in uptake after a relatively high dose of CPZ (9, 96, 161, 174, 299). Doses of 10 mg of CPZ per kg and lower generally do not depress ^{131}I-uptake by the thyroid (8, 96, 299, 300), but Milcou *et al.* (189) found a depression with about 6 mg per kg. Rats on a low-iodine diet seem to be more sensitive to CPZ since 0.5 to 1 mg of the drug per animal decreased the 5-hour ^{131}I-uptake (131).

Inhibitory effects on ^{131}I-uptake may be the result of a central effect or of a direct action of CPZ either on iodine trapping or on peripheral mechanisms. Direct effects of CPZ on synthesis of thyroid hormone in a dose of about 10 mg per kg have been observed by Ksycki and Lockett (161). In a dose of 0.25 mg per mouse (±22 g) CPZ inhibited ^{131}I-uptake by the thyroid, while carcass retention of ^{131}I was increased and urine ^{131}I-excretion was diminished. Incubation of the thyroids of these mice revealed that CPZ inhibited organic binding of ^{131}I. The biosynthesis of tri-iodothyronine and thyroxine was significantly inhibited but formation of mono- and di-iodothyronine was not disturbed. This is the result etiher of a direct action of CPZ in the thyroid or of a central influence of the drug on release of thyroid-stimulating hormone (TSH). Evidence for a direct action of CPZ on the thyroid has been also derived from studies *in vitro* by Mayer *et al.* (179). Incubation of CPZ with thyroid slices depressed ^{131}I trapping by the gland, while later stages of the iodine cycle proceeded abnormally only if high doses were used. The amounts added to the incubation medium indicated that under appropriate conditions CPZ might interfere directly with the synthesis of thyroid hormone *in vivo*.

The amounts of CPZ necessary to reduce ^{131}I-uptake by the thyroid lower

body temperature for about 12 hours (71, 124). A decrease in temperature has been observed without a concomitant reduction in ^{131}I-uptake (300), but Aron *et al.* (8) showed that hypothermia rather than treatment with CPZ causes a decrease in ^{131}I-uptake. In addition, the administration of TSH to rats made hypothermic by placement in a cold environment and treatment with CPZ, fails to stimulate thyroid activity (255). High doses of CPZ also lower blood pressure (269), inhibit excretion of ^{131}I by the kidney, and increase carcass retention of ^{131}I (161, 299). These alterations may cause changes in distribution of ^{131}I in the thyroid. In addition, potentiation of thyroxine by CPZ, presumably by inhibition of its enzymic degradation (287) has been observed. The fact that CPZ decreases basal metabolic rate and counteracts the effect of thyroxine on body temperature (188, 255) further complicates an analysis of the effect of CPZ on thyroid function after a single injection of the drug. Accordingly, results with CPZ obtained by using ^{131}I-uptake should be interpreted with caution.

The rate of release of ^{131}I by the thyroid has for some time been regarded as the most reliable indirect parameter of pituitary-thyroid activity (42). It has been employed by a few investigators for the study of CPZ on thyroid function (96, 108, 189, 246, 300). George and Lomax (108) found that 5 mg of CPZ per kg decreased ^{131}I-release by the thyroid in intact as well as in adrenalectomized rats. Since TSH accelerated ^{131}I-release in CPZ-treated animals, it seemed likely that thyroid activity was not directly blocked by the drug. This finding has been reported by others as well (96, 174). Decrease in rate of release of ^{131}I has been shown after exposure to a variety of stressful stimuli (42, 44, 85, 117) and in response to the administration of adrenocortical steroids (41, 43), but adrenalectomy does not alter the normal rate of release of ^{131}I from the thyroid. The results of George and Lomax (108) in adrenalectomized rats indicate that the blocking action of CPZ on release of ^{131}I by the thyroid is not due to stimulation of glucocorticoid production by the drug (127). From these short-term studies it may be inferred that CPZ, in a dose that, as we have seen, fails to affect ^{131}I-uptake, decreases ^{131}I-release from the thyroid. The depression in thyroid activity may be the result of a reduction in the release of TSH from the pituitary, a direct effect of CPZ on the synthesis of thyroid hormone, or an effect on the action of thyroid hormone.

The effects of chronic treatment with CPZ on thyroid function have been studied with a variety of functional and morphological parameters. A reduction in ^{131}I-uptake by the thyroid in rats chronically treated with CPZ (2 to 100 mg per kg daily) has been demonstrated (9, 188, 214, 237, 299, 300). ^{131}I-release from the thyroid is similarly depressed by chronic treatment (96, 246, 300). The effect seems to depend on the dose used since CPZ given twice a day for 3 days inhibited ^{131}I-release in doses of 20 mg per day but not if 5 mg per day was administered (96). These results suggest that thyroid function is blocked in animals on long-term treatment with CPZ. However, not all experiments are consistent with a reduction in thyroid function in animals treated chronically. Arvay *et al.* (9)

showed that 40 to 100 mg of CPZ per kg injected daily inhibited uptake of ^{131}I by the gland 3 hours or 2 days after onset of the treatment, had no effect after 10 days of treatment, and increased the uptake after 30 days of treatment. A similar phasic effect of CPZ was noted by other workers (37). In rats treated with CPZ for 12 days ^{131}I-uptake was depressed during the first 3 days of treatment and increased during the next 9 days (237). This rise was more significant if higher doses were used. Pantić *et al.* (214) found that whereas 2 and 10 mg of CPZ per kg did not affect ^{131}I-uptake, 25 mg per kg increased the trapping of the radioactive iodide. In rabbits treated for 3 weeks with 4 mg per kg CPZ daily serum protein-bound iodine was increased (172).

Other parameters of thyroid function suggest a depression of activity of the gland in animals under chronic treatment with the drug. Milin and Stern (190) demonstrated that 2.5 mg of CPZ per kg for 7 to 14 days prevented manifestations of hyperthyroidism in captured hares exposed to barking dogs. A reduction in O_2-consumption and hormone content in the thyroid and TSH activity in the pituitary (3, 188) and histological signs of thyroid inactivity (255) have been observed in rats treated for some time with CPZ. The goitrogenic effect of methylthiouracil (3) and of propylthiouracil (183) is partly prevented by CPZ treatment. However, CPZ itself may cause goiter. Sulman (271) showed hypertrophy of the thyroid and a decrease in basal metabolic rate in male and female rats treated for 3½ months with 10 mg of CPZ per kg daily. This would suggest a direct effect of the drug on the thyroid, but no further relevant data were provided. CPZ administered in a low-iodine diet induced goiter, but in female rats only. Oophorectomized rats fed a similar diet for 2 weeks showed goiter only if 10 μg of estradiol were given every other day. In contrast, Reiss (237) and Radde and Kalow (234) observed reduction in thyroid weight. The latter authors in a meticulous study showed that feeding rats a less potent phenothiazine derivative, levopromazine, in doses of 20 to 25 mg per kg daily for varying periods of time caused a reduction in thyroid weight, a decrease in ^{131}I content of the thyroid 24 hours after tracer administration, and a decrease in thyrotropic cells in the pituitary gland. Renal excretion of ^{131}I in chronically treated rats was accelerated and plasma ^{131}I was decreased. Thus renal effects interfered with ^{131}I-uptake by the thyroid. It was concluded that the drug interfered with the synthesis of thyroid hormone. The decrease in β-cells in the pituitary as a result of treatment suggested that the depression in thyroid activity was due to reduction in TSH release.

The effects of CPZ may depend on the experimental situation in which the drug is studied. For example, characteristic changes in the thyroid after intense emotional stress, *i.e.*, an increase in activity followed by a return to normal and finally to hypofunction, are prevented by CPZ treatment (9). Similarly Földes *et al.* (96) found that CPZ inhibited the reduction in ^{131}I-uptake elicited by formalin stress.

Chronic treatment with CPZ depresses thyroid activity. This effect may disappear or even be reversed, depending on the dose, the duration of the treatment,

and the experimental situation. Whether these alterations are solely caused by differences in the rate of release of TSH from the anterior pituitary remains to be clarified.

C. Pituitary-adrenal axis

Most of the reports on the effect of CPZ on pituitary function concern the action of the drug on the pituitary-adrenal system. The results are conflicting and, in spite of the abundance of papers, the influence of CPZ on this system is still not clear. Inhibition of stress-induced ACTH release as well as release of ACTH by the drug itself have been observed in animals and man.

Aron *et al.* (7) were the first to observe inhibition of stress-induced discharge of ACTH in rats treated with CPZ. Doses of 10 and 50 mg per kg were used and depletion of adrenal ascorbic acid (AAD) was the index of ACTH release. These amounts suffice to stimulate pituitary-adrenal activity (116, 127, 157, 164, 203, 210, 249, 268). Castaigne (46) also found that CPZ blocked AAD induced by stress in rats. Mahfouz and Ezz (173) found that CPZ in a dose of 2 mg per kg in rats prevented the usual AAD that follows stress from heat, cold or ether. Ascorbic acid concentration of adrenals of CPZ-treated rats was fairly low. The stress did not further deplete the gland of ascorbic acid.

Incomplete inhibition of stress-induced ACTH release was shown by Hamburger (116); in a dose of 100 mg per kg in rats 2 hours before the stress of laparotomy, CPZ markedly prevented AAD, although the drug itself had already caused a significant depletion. Cheymol *et al.* (57) found that 10 and 50 mg of CPZ per kg partially prevented AAD after formalin stress.Řežābek and Votava (238) also observed a partial inhibition of AAD in rats treated with 20 mg of CPZ per kg 2 times within 1 hour before the stress of unilateral adrenalectomy. A partial block of AAD was found in rats exposed to heat stress treated with 20 mg of CPZ per kg (136) and in rats treated with 5 mg of CPZ per kg and subjected to shaking either at room temperature or at a high temperature (137). The blocking action was correlated with the effectiveness of CPZ in protecting against fatal effects of heat stress.

Holzbauer and Vogt (127) failed to find blockade of AAD in response to surgical stress in rats treated with 10 mg of CPZ per kg 3 hours before the operation. These authors concluded that the experiments did not substantiate the hope expressed by Aron *et al.* (7) that CPZ might produce a kind of hypophysectomy.

With 2.5 mg of CPZ per kg, which in itself did not stimulate release of ACTH, Nasmyth (204) failed to prevent AAD after adrenaline, surgical stress, or high doses of histamine. The effect of small doses of histamine on AAD was inhibited. However, with 3 mg of CPZ per kg 60 minutes before stress, Van Peenen and Way (220) observed inhibition of adrenaline-induced AAD but not that of histamine or aspirin. Morphine-induced depletion of adrenal ascorbic acid was partially prevented by CPZ. Klepping *et al.* (152) also found AAD after adrenaline weaker in rats treated with CPZ than in controls. The adrenolytic and antihistaminic activities of CPZ (71, 243) may well account for its effects on the release of ACTH induced by adrenaline and histamine.

The reports show that CPZ abolishes, partially prevents, or fails to block stress-induced release of ACTH. In most of the studies, AAD was a parameter of pituitary-adrenal activation. AAD is a reliable index of the release of ACTH only when the adrenal gland is at rest and contains high concentrations of ascorbic acid (289). Accordingly, the initial stimulating effect on ACTH release with the subsequent AAD may obscure a further stimulation caused by the stress. Another possible explanation of the discrepancy in results may be found in the hypothermic effect of CPZ (71, 124). Georges and Cahn (109) suggested that hypothermia is the important factor in the blockade of stress-induced ACTH release. Aron *et al.* (8) showed that AAD in response to unilateral adrenalectomy was blocked by pretreatment with 10 mg of CPZ per kg but was not inhibited in hypothermic rats with a core temperature between 15° and 20°C. Curiously, like Georges and Cahn (109), Aron *et al.* (8) found blockade only in rats with body temperature between 25° and 27°C. The controversy as to the existence of CPZ-induced blockade of the pituitary-adrenal response to stress might therefore be explained by assuming that marked differences have existed in environmental temperature under which the experiments were performed. Since nearly none of the papers reviewed reported the body temperature of CPZ-treated animals at the time stress-induced release of ACTH was studied, evidence for or against this assumption is lacking.

The stimulating action of CPZ on pituitary-adrenal activity was first recognized by Georges and Cahn (109) and Holzbauer and Vogt (127) and later confirmed by many others. In his excellent review, Munson (201) calculated that amounts higher than 20 mg per kg stimulated ACTH release in unanesthetized rats. However, more direct parameters of adrenocortical activity have revealed that doses as low as 2 mg of CPZ per kg already elicit a rise in pituitary-adrenal activity (165, 268). Hamburger (116) found a dose-response relationship between CPZ and AAD, and Sapeika (248), using doses as high as 300 mg per kg by mouth, found an AAD lasting 3 to 6 hours. Kovács *et al.* (157) showed that 15 mg of CPZ per kg in rats caused a significant AAD. Further depletion of AAD in response to intraperitoneally administered hypertonic saline was not blocked. Interestingly, the nuclear hypertrophy observed in the zona glomerulosa as a result of salt loading was blocked by CPZ. Nagata (203) reported a significant AAD with 8 mg of CPZ per kg. Lammers (164), using the rate of steroid production by excised adrenal tissue as a parameter of pituitary-adrenal activity, also demonstrated stimulation of ACTH release by CPZ in a dose-dependent manner. Egdahl *et al.* (88), Egdahl and Richards (87), and Betz and Ganong (25) observed an increase in circulating adrenal steroids after CPZ in dogs, Sasaki (249) in guinea pigs, and Harwood and Mason (119) in monkeys. Egdahl and Richards (87) showed that the rise in 17-OH-steroids in the adrenal effluent was abolished in hypophysectomized dogs; this indicates that the action of the drug is not at the adrenal gland directly.

The stimulating action of CPZ on ACTH release was carefully analyzed by Smith *et al.* (268). These authors showed that sedative doses of CPZ elicited ACTH release as measured by AAD and plasma corticosterone. Nonsedative

TABLE 1

Effect of stress on pituitary-adrenal activity of male rats 12 hours after a single subcutaneous injection of 50 mg of chlorpromazine per kg

Treatment	Corticosterone production *in vitro* μg/100 mg adrenal/hr		
	Nonstressed	Strange environment	Ether anesthesia
Saline	2.6 ± 0.5[a]	9.7 ± 0.9	12.5 ± 1.0
	P<.01	P<.05	P<.01
Chlorpromazine	6.2 ± 0.5	6.9 ± 0.8	8.1 ± 1.4

[a] Standard error of the mean. Mean of 8 observations.

amounts did not affect pituitary-adrenal activity. High doses of CPZ caused a persistent release of ACTH and reduced ACTH content in the pituitary. In animals with a persistent ACTH release induced by 3 injections of 20 mg of CPZ per kg spaced 8 hours apart, the effect of cold stress was markedly reduced. This blocking action was explained on the basis of exhaustion of pituitary ACTH stores. In a similar study by Lammers (164) a single subcutaneous injection of 50 mg of CPZ per kg elicited an ACTH release that lasted for at least 18 hours. Exposure of rats with CPZ-induced persistent ACTH release to ether stress or to the emotional stress of transfer to a strange environment, 12 hours after the injection of the CPZ, did not significantly increase ACTH release from the pituitary, as determined by the rate of corticosterone production by rat adrenal tissue *in vitro* (table 1).

In CPZ-treated rats hypophysectomized 2 hours before 2 test doses of ACTH, the sensitivity of the adrenal cortex to ACTH appeared to be moderately increased (164). Pituitary ACTH content was not affected 12 hours after the injection of 50 mg of CPZ per kg. Accordingly, the reduction in adrenal response to stress in CPZ-treated animals could not be due to exhaustion of ACTH stores. However, the sensitivity of the anterior pituitary to a crude corticotrophin-releasing factor and to vasopressin used as a corticotrophin releaser was significantly decreased (31, 164). Inhibition by CPZ of stress-induced release of ACTH release could thus be explained by refractoriness of the anterior pituitary to corticotrophin releasers. That this refractoriness was not merely the result of long-term nonspecific stimulation of ACTH release by CPZ was shown by the fact that the sensitivity of the anterior pituitary to vasopressin was not diminished in rats in which bilateral nephrectomy had caused about the same increase in pituitary-adrenal activity as in CPZ-treated rats (31).

Shuster and Hanna (263) showed that CPZ depresses incorporation of amino acids into brain cells of rats; this indicates a depressed protein synthesis. This effect could be abolished by placing the animals in an environmental temperature of 35°C. However, in rats kept at 35° ± 2°C during the 12 hours of treatment with the 50 mg per kg dose of CPZ, the anterior pituitary exhibited the same reduced responsiveness to vasopressin as that of animals kept at 22° ± 1°C (De Wied, unpublished observations). Relatively small bilateral lesions in the

anterior median eminence prevented the inhibitory effect of CPZ on vasopressin-induced release of ACTH; the lesion did not interfere with the stimulatory action of CPZ on ACTH release (31). These results suggest that CPZ may at the same time activate and inhibit release of ACTH and that these 2 phenomena can be separated by a lesion in the anterior median eminence of the hypothalamus. The results are at variance with those of Smith *et al.* (268), who found a marked depletion of ACTH from the pituitary after CPZ treatment. The facts that these authors gave slightly more CPZ and measured pituitary ACTH content 20 hours, instead of 12 hours, after injection of the drug may explain the discrepancy. It is worth noting that Reiss (236), with a single injection of 4 mg of CPZ, found a slight increase in anterior pituitary ACTH for several days. In addition, a low ACTH content in the pituitary does not necessarily mean that ACTH release cannot be stimulated. Vernikos-Danellis (286) showed that pituitaries low in ACTH can still release ACTH. Interestingly, Knigge *et al.* (155) reported that the temporary block in ACTH release during severe stress was removed by lesions of various loci around the median eminence. Kitay *et al.* (150), who found effects on ACTH release with reserpine and adrenaline like those observed by Smith *et al.* (268) with CPZ, explained the inability of the drug-treated rats with persistent ACTH release to respond with an immediate release of ACTH by the absence of readily available ACTH for immediate release, leaving chronic hypersecretion of ACTH unimpaired. For a more detailed discussion on the significance of pituitary ACTH stores for release of ACTH the reader is referred to the review of Munson (201).

Many reports appeared as to the occurrence of adrenal hypertrophy after chronic treatment with CPZ (10, 25, 128, 210, 236, 271, 278). Tolerance to the corticotrophic effect of CPZ does not seem to develop. In addition, chronic treatment with the drug does not protect or only slightly diminishes pituitary-adrenal response to stress. This holds for the rat as well as for the dog.

A low dose of CPZ, which causes a brief stimulation of pituitary-adrenal activity, blocks the animal's behavioral response to emotional stimuli (165, 270). Two hours after the injection of 2 mg of CPZ per kg, adrenal activity is almost normal again while the tranquilizing action of the drug reaches its maximum effect at that time. If rats so treated, and clearly sedated, are exposed to emotional stimuli like transfer to a strange environment, sound, pain, or a conditioned emotional stress, ACTH release is not impaired except for the corticotrophic effect of pain stress, which is slightly reduced. Similar results were obtained by Betz and Ganong (25) in the dog using immobilization as a stress. Pekkarinen *et al.* (221) reported that CPZ in moderate doses failed to inhibit neurogenic stress, induced by exposing rats to dogs and cats. Higher doses, which themselves increased circulating corticosterone, reduced the pituitary-adrenal response to neurogenic stress. Chronic administration of CPZ to guinea pigs did not reduce the effect of a similar neurogenic stress as determined by urinary 17-ketosteroid excretion. Accordingly, in unanesthetized rats, CPZ in relatively small amounts, such as cause tranquilization, cannot reduce or block the effect of emotional stress on ACTH release from the pituitary.

Several authors have tried to overcome the stimulatory action of CPZ on ACTH release by pretreating the rats with pentobarbital (Nembutal) before giving CPZ, or by daily treatment with CPZ to obtain tolerance to the stimulatory effect or by injecting very low doses of CPZ, which do not stimulate or only slightly stimulate pituitary-adrenal activity (10, 25, 166, 210, 260). Administration of 20 mg of CPZ per kg in rats pretreated with anesthetic doses of pentobarbital blocked the effect of histamine, adrenaline, noradrenaline, and unilateral adrenalectomy on AAD (210). Adrenal responsiveness to ACTH was unaffected by CPZ. Sevy *et al.* (260) reported similar results and in addition showed that the effect of pitressin in rats treated with pentobarbital and CPZ was not blocked. Since pitressin possesses corticotrophin-releasing activity, the site of the action of pentobarbital-CPZ block may be located in the brain. In an attempt to reinvestigate the effect of stress in rats treated with pentobarbital and CPZ, using the rate of corticosterone production by excised adrenal glands as an index of ACTH release, CPZ in a dose of 20 mg per kg injected subcutaneously 15 minutes after an intraperitoneal injection of 42 mg of pentobarbital sodium per kg completely blocked the ACTH release by histamine, nicotine or unilateral adrenalectomy (164, 166). This amount of CPZ and even doses up to 50 mg per kg did not stimulate ACTH release in rats anesthetized with pentobarbital. The sensitivity to ACTH of the adrenal cortex of rats anesthetized with pentobarbital and treated with 20 mg of CPZ per kg was similar to that of animals anesthetized with pentobarbital only and to that of hypophysectomized rats. Lysine vasopressin in amounts of 300, 900 and 2700 mU per kg stimulated pituitary-adrenal activity in rats treated with pentobarbital and CPZ much as in animals treated with pentobarbital without CPZ. Since lysine vasopressin can release ACTH in the rat made unresponsive to noxious stimuli by destruction of the median eminence (see for review 103), the results indicate that the blocking action of pentobarbital plus CPZ is located in the brain.

Betz and Ganong (25) failed to record a change in adrenal venous 17-hydroxysteroid output in surgically stressed dogs after injection of 2.5 mg CPZ per kg followed by a 30-minute infusion of the same amount. It might be that the dose of CPZ was not sufficient to block the release of ACTH and that the stress was too strong. In fact, ACTH release may be stimulated in the pentobarbital-CPZ blocked rat during severe surgical stress (De Wied, unpublished observations). Thus, in the rat the combination of pentobarbital and CPZ blocks stress-induced ACTH release. Pentobarbital alone can inhibit pituitary-adrenal activity in response to mild stimuli only (38, 143, 208, 253). Severe stresses like surgical trauma and the injection of substances like the catecholamines, serotonin, carbachol, nicotine, *etc.*, in sufficient amounts break through the pentobarbital block. The combination with CPZ also inhibits the corticotrophic effect of the latter category of stresses although very severe noxious stimulating may not prevent stimulation of ACTH release.

The anesthetic action of pentobarbital is potentiated by CPZ (71). Brodie *et al.* (39) showed that CPZ sensitizes the central nervous system toward the action of pentobarbital and these workers regarded CPZ as a "true potentiator."

Lessin and Parkes (168), however, thought that CPZ affects the metabolism of pentobarbital. Be this as it may, CPZ also potentiates the inhibitory effect of pentobarbital on stress-induced ACTH release. Whether or not intrinsic inhibitory effects of the drug on ACTH release come into play cannot be determined. In this respect it is worth mentioning that the combination pentobarbital-mepazine has a much weaker inhibitory effect on stress-induced ACTH release than pentobarbital-CPZ (211), and that potentiation of anesthesia by mepazine is also much weaker (279).

D. Growth hormone

Treatment with daily doses of 2.5 mg per kg of CPZ administered by mouth for 4 weeks does not affect body weight in male and female rats (183). In a strain (ZBC) of mice fed 0.3 % of CPZ for a considerable time growth was retarded (74). In rats treated for 3½ months with 10 mg of CPZ, growth was stunted (271). Administration of growth hormone returned the gain of body weight to normal. From this experiment it was inferred that CPZ blocks release of growth hormone. In fact Müller *et al.* (200) found that CPZ inhibited depletion of growth hormone in the pituitary in response to insulin hypoglycemia. This result, however, may be also explained by an anti-insulin action of CPZ (32, 51, 135, 207, 243). Meyer and Knobil (187), measuring growth hormone in blood by a radioimmunoassay, found that CPZ in a dose of 1.2 to 1.5 mg per kg induced a large increase in circulating growth hormone in the monkey. These doses effected a marked tranquilization. Long-term experiments were not performed. The latter results indicate that CPZ stimulates release of growth hormone as it stimulates release of ACTH. In this respect it is worth mentioning that growth hormone release is affected by the same stimuli as ACTH release (160, 187, 219).

II. CHLORPROMAZINE AND THE INTERMEDIATE LOBE OF THE PITUITARY

A. Melanocyte-stimulating hormone

A few papers were found in the literature on the effect of CPZ on melanocyte-stimulating hormone (MSH). Scott (257) showed that CPZ causes melanophore dispersion in the normal frog and in the sand dap. Scott and Nading (258) further showed that CPZ and related phenothiazines, with the exception of mepazine, cause melanophore dispersion in normal frogs. Since all drugs tested were without effect in hypophysectomized frogs, it was concluded that these compounds bring about release of MSH either by a direct action in the pituitary gland or indirectly *via* the brain. The possibility was also recognized that the effect could be due to potentiation of MSH instead of release of active hormone. However, one of the drugs used (fluphenazine) did not delay paling when injected into frogs shortly after hypophysectomy when circulating MSH is still present.

Evidence for an effect of CPZ on pituitary MSH in rats was provided by Kastin and Schally (140). These authors showed that the MSH content in the pituitary of rats treated with various phenothiazines decreased. In these rats injection of MSH or MSH-release-inhibiting factor resulted in pituitary MSH levels higher

than those of rats treated with the phenothiazine only. Since hypothalamic lesions in the frog decrease the MSH content of the pituitary (139) and addition of hypothalamic extracts to rat pituitaries *in vitro* similarly decreases pituitary MSH, the results indicate that the phenothiazines act in the hypothalamus. As in the case of prolactin release (186), the phenothiazines seem to operate by removing central inhibitory influences on MSH-release.

III. CHLORPROMAZINE AND THE POSTERIOR LOBE OF THE PITUITARY

A. Antidiuretic hormone

Most of the studies done with regard to the posterior lobe are on the effect of CPZ on the release of antidiuretic hormone (ADH). The drug induces antidiuretic as well as diuretic effects, and its action on ADH release is not clear (107).

Meier *et al.* (184) were the first to report the antidiuretic action of CPZ in hydrated rats. A relationship between dose and antidiuretic response was found. The dose-response curves of pitressin and CPZ, however, did not run parallel. When the rats were hydrated with 0.9% NaCl instead of water, the antidiuretic effect of both pitressin and CPZ disappeared. A relationship between dose and antidiuretic effect was also found by Supek *et al.* (273) with amounts of CPZ of 1 to 20 mg per kg. CPZ had nearly no effect on chloride excretion. In addition, in rats anesthetized with alcohol a very low dose of CPZ (0.05 mg per kg) elicited a marked antidiuresis while in rats with diabetes insipidus the antidiuretic effect of CPZ was no longer demonstrable. The latter observation suggests that the antidiuretic effect of CPZ is due to increased release of ADH. Kovács *et al.* (158) showed that 1.5 mg of CPZ per kg caused a brief antidiuretic effect in hydrated rats. A dose of 2.5 mg of CPZ per kg elicited an evanescent inhibition of water diuresis in the rat hydrated with 0.2% NaCl solution (293). Since CPZ potentiates the action of ADH, a peripheral mode of action for the antidiuretic effect of the drug was suggested (158). This is in accord with the findings of Supek *et al.* (274) that CPZ in doses of 0.08 and 10 mg per kg significantly potentiated the antidiuretic action of nicotine and of posterior pituitary extract. Interestingly, the higher dose of CPZ reduced the chloruretic effect of these 2 substances, a phenomenon which has been ascribed to an action of oxytocin on the kidney (40). Tiwari *et al.* (280) further showed in the hydrated rat that substitution of the propyl group by an ethyl group in the side chain may reverse the antidiuretic action of CPZ and induce water diuresis.

In contrast to most investigators, Dasgupta, (79) failed to find an effect of CPZ on urine excretion in hydrated rats. The drug was injected in a dose of 5 mg per kg half an hour before water loading. Since the antidiuretic action is evanescent, the timing of the experiment may have obscured an antidiuretic action. However, Bachrach *et al.* (16) found that 10 mg of CPZ per kg 2 hours before hydration induced a sustained antidiuresis. Boris and Stevenson (33) found that 8 or 10 mg of CPZ per kg injected into rats 1 hour before water loading induced a significant antidiuresis while 4 mg per kg did not. These authors compared structurally unrelated psychodepressants and considered the intensity of their anti-

diuretic effects to be related to the severity of CNS depression they elicited. In this respect it is of interest to note that Jacobson (130) found that lesions in the septal area of rats, which cause a primary polydipsia, sensitized the animal toward the antidiuretic effect of CPZ but not that of pitressin.

Studies of the rate of urine excretion in hydrated animals indicate that CPZ in sedative amounts may inhibit water diuresis. Marked hemodynamic changes may occur as a result of the treatment with CPZ (269). In addition it causes renal ischemia in rabbits (16). These changes suffice to explain the transitory antidiuretic action of CPZ.

ADH release, however, may take place after the acute administration of CPZ and related drugs. Khazan *et al.* (145) used the increase in water uptake through the skin of amphibians as a bioassay of mammalian ADH. CPZ and other phenothiazines promoted water uptake through the skin of *Bufo viridis* and *Rana pipiens*. The effect was similar to that of pitressin or pituitary homogenates, although the action of the phenothiazines was of much longer duration. Hypophysectomy almost completely prevented the effect. Thus, the influence of the phenothiazines on water uptake through the skin is mediated by the pituitary. Potentiation of circulating ADH was not excluded as a possible explanation.

Several studies have been done with more direct parameters of activity of the hypothalamo-neurohypophyseal system. Kivalo *et al.* (151) found that 25 mg of CPZ per kg for 7 days to rats reduced neurosecretory material in the neurohypophysis but not in the supraoptic and paraventricular nuclei. Animals treated with the drug drank less water but produced more urine. Antidiuretic activity in blood was less in CPZ-treated rats. According to these authors CPZ depresses the hypothalamus, inhibits thirst and reduces release of ADH. Bachrach *et al.* (16), working with lower doses, found no effect of 10 mg of CPZ per kg daily for 6 days on neurosecretory material in the neurohypophysis. Depletion of neurosecretory material during dehydration was not affected by CPZ treatment. A 2% saline solution given by mouth to rabbits induced a decrease in the number of cells and in the size of the cells and granules in the hypothalamus. This was not seen in animals treated with CPZ. Moses (195) found that daily administration of 20 mg of CPZ per kg inhibits the pituitary depletion of ADH that normally occurs during water deprivation for 48 hours. These amounts of CPZ also prevent depletion induced by hypertonic saline. The rate of reaccumulation of ADH in rat pituitaries at the end of the water deprivation period was unaffected by CPZ. Interestingly, administration of CPZ to adrenalectomized rats maintained on desoxycorticosterone and isotonic saline failed to inhibit dehydration-induced depletion of ADH. Since glucocorticoids inhibit ADH release (181, 295) and counteract the osmotic stimulus to ADH release presumably by a renal effect (194), the results may be partly explained by the stimulatory effect of CPZ on the pituitary-adrenal system (127). Shibusawa *et al.* (262) found that increased neurosecretory activity in the supraoptic and paraventricular nuclei of the hypothalamus observed after scalding in dogs was prevented bypretreatment with 2.5 mg of CPZ. In hydrated rats 2.5 mg of CPZ per kg prevented the antidiuretic response to painful stimuli but not to histamine or nicotine, which

are thought to act in the hypothalamus (293). These results suggest that CPZ inhibits central mechanisms involved in pain or emotion rather than the hypothalamic neurons that produce and secrete ADH. In this respect it is worth mentioning that CPZ in very high doses prevents EEG arousal in response to painful stimulation (281).

The studies cited above indicate that CPZ may cause a brief stimulation of ADH release. In high amounts given over several days CPZ may depress synthesis of ADH and in lower dose levels may inhibit ADH release in response to hypertonic salt loading or to painful stimuli. Until the influence of CPZ on antidiuretic activity in the circulation has been accurately assessed, the action of the tranquilizer on ADH release cannot be determined with certainty.

B. Oxytocin

Not much is known about the effect of CPZ on release of oxytocin. Chaudhury (54) found that CPZ in a dose of 5 mg per kg blocks milk ejection in the lactating rat. The fact that administration of oxytocin overcomes the block, suggests that inhibition of milk ejection is caused by inhibition of oxytocin release. Since doses of CPZ lower than 0.5 mg per kg did not prevent reflex release of oxytocin, the injection *per se* could not have acted as a nonspecific stress, for this is known to block milk ejection (76). Neither ADH nor ACTH blocked milk ejection. In another study Chaudhury *et al.* (55) showed that CPZ in a dose of 2.5 mg per kg reduced stress-induced block of milk ejection in the guinea pig. Since Cross (75) has shown that adrenaline released during stress may be responsible for the blockade of milk ejection, the adrenolytic action of CPZ might have been responsible for inhibition of the stress-induced block. However, Chaudhury *et al.* (55) showed that neither α- nor β-adrenergic blockers inhibit the stress-induced block. The action of CPZ may be located in the brain, where it may weaken the effect of stress and prevent inhibition of oxytocin release. Depletion of oxytocin in the posterior pituitiary in response to scalding was found to be inhibited in dogs pretreated with 100 mg of CPZ (262). In a recent study Yokoyama and Sawyer (301) failed to observe CPZ-induced block of milk ejection in the lactating rat. Pups suckling mothers treated with 5 or 10 mg of CPZ per day could obtain as much milk in 2 hours as those of nontreated control mothers. These results are at variance with those of Chaudhury *et al.* (55). In the studies of the latter worker, the effect of CPZ was determined 25 minutes after injection of the drug while Yokoyama and Sawyer (301) treated the animals for 5 days. Effectiveness of the treatment was judged by sedative effects on the mother, signs of pseudopregnancy, and maintenance of mammary function after weaning. However, in the experiments of Yokoyama and Sawyer (301) milk ejection of placebo-treated mothers declined at a faster rate during the 5 days of observation than that of nontreated controls. This may be the result of the stress of handling and injection which may have been reduced by CPZ.

The reports which have appeared indicate that CPZ may block the release of oxytocin. However, firm conclusions have to await results in which more direct parameters of oxytocin activity in the circulation are studied.

IV. CLINICAL EFFECTS OF CHLORPROMAZINE ON ENDOCRINE FUNCTION

Clinical studies with CPZ have been performed mainly in patients with psychiatric disorders. The results may therefore be clouded by changes which take place after treatment with CPZ. An interesting study by Friedell (100) demonstrates the influence of the state of the patient on the results obtained when psychotropic drugs are given. Patients in a chronic tension state had a higher-than-normal ^{131}I-uptake by the thyroid. In a double-blind study with 12 patients treated with meprobamate with or without benactyzine or with a placebo, when the tension, nervousness and excitement of the patients subsided as a result of treatment, ^{131}I-uptake by the thyroid was brought back to normal. Accordingly, relief of anxiety and tension by treatment with the drug may not necessarily reflect influences of CPZ on pituitary function.

A description of the most common clinical effects of CPZ are given below. Effects on gonadal, on thyroid and on adrenal function are treated in subsequent order, followed by a brief survey of the influence of CPZ on ADH release.

That CPZ may affect the pituitary-gonad axis in man much as it does in animals has been shown by Whitelaw (296), who studied the effect of CPZ on ovulation in regularly cycling patients and found that an injection of 25 mg of CPZ twice daily 1 to 3 days before ovulation, as assessed by morning temperature and endometrial biopsies, postponed menstruation for 8 to 16 days. Administration of CPZ at the end of the cycle did not delay menstruation. Accordingly, it can be deduced that in women, as in animals, CPZ blocks ovulation and enhances secretion of prolactin.

Therapy with CPZ is associated with menstrual irregularities, amenorrhea and galactorrhea. Many reports have appeared on the effect of CPZ on gonadal function in female patients (13, 60, 63, 72, 82, 93, 101, 106, 122, 146, 162, 175, 225, 234, 240, 299). Most observations were done in mentally ill patients. The most frequent disturbance found is amenorrhea and menstrual irregularities. Amenorrhea seems to be accompanied by galactorrhea in 80% of cases (82). It is seen only in patients treated with relatively high doses of the drug (13, 82, 162). The amenorrhea may last several months or may disappear spontaneously either when the treatment is stopped or when the dosage of CPZ is reduced.

The frequency with which galactorrhea occurs varies considerably. It is found in women more often before than after the menopause (82) and it can be observed 8 to 30 days after onset of the treatment with doses between 25 and 600 mg daily (see review 20). For example in a study with 145 psychiatric patients, Py and Mathieu (233) found that more than 70 had galactorrhea while Robinson (239) found galactorrhea in only 7 out of 66 patients treated with large doses of CPZ. Khazan *et al.* (146) found galactorrhea in 33 cases of 650 psychiatric patients treated with CPZ. Of the phenathiazines used, trifluprazine proved to cause a higher incidence of galactorrhea than CPZ.

Vaginal smears of patients treated with CPZ indicate estrogen deficiency (63, 162, 225). Colmeiro-Laforet (63) observed proliferation in endometrial biopsies in 2 women, 21 and 60 days after the last menstruation. Curiously, the administration of progesterone induced bleeding in one of the patients but administra-

tion of estrogen did not. FSH excretion in the urine was normal in patients treated with 150 to 200 mg and increased with doses between 300 and 400 mg of CPZ (225). However, Hauser *et al.* (122) reported a decrease in FSH excretion in women treated parenterally with 200 to 500 mg of CPZ daily. 17-Ketosteroid excretion in the urine is within normal limits (225) or relatively low in patients treated with fairly high doses of CPZ (122, 225). Urinary pregnandiol excretion may be also decreased (122). These observations need to be extended. Conclusions as to the mode of action of CPZ with respect to the induction of amenorrhea and galactorrhea have to await careful analysis of gonadal activity in the human being with more sophisticated methods.

A number of studies indicate that CPZ may decrease signs of hyperthyroidism. CPZ in combination with mild hypothermia gave steady falls in pulse rate, temperature, and other signs of thyrotoxicosis (86, 129). In 2 myxedematous patients CPZ induced hypothermic coma within a short time (134). However, in euthyroid and hyperthyroid patients treated with 200 mg of promazine daily for 10 to 21 days, ^{131}I-uptake, serum protein-bound iodine and cholesterol levels did not change (206). Lövei *et al.* (172) similarly failed to find an antithyroid effect of CPZ in hyperthyroid patients.

In schizophrenic patients, amounts of 100 to 400 mg of CPZ daily given alone or in combination with imipramine did not appreciably affect ^{131}I-uptake, serum protein-bound iodine, cholesterol or basal metabolic rate (22). Reichlin *et al.* (235) treated schizophrenic patients with 2000 mg of CPZ daily in addition to other drugs for 30 days. These patients slept for 20 hours a day. In spite of these extremely high doses of the drug, serum protein-bound iodine was not changed; but thyroxine turnover was accelerated during the last 10 days of treatment. If ambulatory psychiatric patients were treated daily with 600 mg of CPZ, a decrease in protein-bound iodine was found, indicating a decrease in thyroid hormone production. In contrast, in 20 psychotic patients with a normal thyroid function Crammer and Pover (73) found no significant increase in ^{131}I-uptake after giving them 300 mg of CPZ daily for 3 months. In a study with 123 patients Blumberg (28) found that CPZ caused an increase in ^{131}I-uptake. Amounts of 300 mg of CPZ plus 3.75 mg of procyclidine were given daily and were augmented successively at weekly intervals up to 1200 mg of CPZ plus 15 mg of procyclidine. The latter drug was administered to prevent extrapyramidal symptoms eventually caused by CPZ. Procyclidine alone did not alter ^{131}I-uptake. These results indicate increased iodide trapping as a result either of increased TSH release or of recirculation of the iodide. Alterations in renal clearance or iodide, especially in patients treated with high doses of CPZ, may account for recirculation and the consequent increase in uptake. Perry and Hughes (222) showed that decrease in the renal excretion of iodide in renal disease may result in an increase by the thyroid. Increased uptake of ^{131}I is also seen in liver disease (199), and since chronic treatment with CPZ may cause liver damage, alterations in ^{131}I-uptake may be the result of this effect.

The pituitary-adrenal axis may be also affected by CPZ. A decrease in circulating adrenal steroids has been reported after treatment with CPZ in doses

between 300 and 450 mg daily (67). A decrease in excretion of adrenocortical steroids in the urine during CPZ treatment was found by several authors (24, 67, 149, 224, 272). However, orally administered CPZ failed to affect 17-keto- or 17-hydroxysteroids in the urine whereas intramuscularly injected CPZ had a transitory inhibitory effect (99). With high doses of CPZ Mefferd *et al.* (182) failed to observe a decrease in urinary excretion of 17-ketosteroids or 17-hydroxysteroids. Kinberger *et al.* (149) found that intravenous injection of CPZ causes a fall in circulating eosinophils, and Gold *et al.* (112) observed a moderate increase in urinary 17-hydroxysteroid excretion. Both observations indicate a stimulation of ACTH release.

Inhibition of stress-induced pituitary-adrenal activity in man by CPZ was reported by Christy *et al.* (58). The rise in circulating adrenal steroids induced by insulin coma was inhibited by CPZ. The drug increases blood glucose levels in animals and counteracts insulin hypoglycemia (32, 51, 135, 207, 243). In addition it causes an abnormal glucose tolerance curve in patients (51). However, Hasselblatt and Shuster (120) found that although CPZ inhibited hypoglycemia caused by tolbutamide, it did not affect insulin hypoglycemia. In fact, Christy *et al.* (58) found that CPZ did not affect insulin hypoglycemia while blocking insulin-induced ACTH release. Kinberger *et al.* (149) failed to find inhibition of eosinopenia during fever or after injection of adrenaline in patients treated with CPZ. Fotherby *et al.* (99) found that the corticotrophic effect of typhoid vaccine was partly inhibited in schizophrenics treated with CPZ. Since the adrenal response to ACTH was similarly depressed, it would appear that CPZ had a direct action on the adrenal cortex. Gold *et al.* (112) found the increase in circulating ACTH, induced by methopyrapone in patients to be reduced by CPZ. The effect of ACTH in patients treated with methopyrapone was also reduced. Sloane *et al.* (265) also reported adrenal responsiveness to ACTH depressed in CPZ-treated patients. Some authors, however, found a normal adrenal response to ACTH (58, 149, 156) in patients treated with CPZ. The pituitary-adrenal response to surgical stress does not seem to be affected by treatment with CPZ (58, 112, 283). Kothari *et al.* (156) found that CPZ inhibited eosinopenia after heat stress in psychiatric patients.

Not much is known of the effect of CPZ on posterior pituitary activity. Some influences of the drug have been described on release of ADH.

Diuretic effects of CPZ have been found in patients. Cohen (61) showed that 3.5 mg of CPZ infused in approximately 2 hours caused a significant diuresis in normal persons as well as in patients with cor pulmonale or congestive heart failure. The diuresis was not accompanied by increased electrolyte excretion. These small amounts of CPZ did not affect blood pressure. Diuretic effects of CPZ were also reported by Moyer *et al.* (196). Parrish and Levine (216) found a marked effect on renal hemodynamics when 25 mg of CPZ were given intravenously. It reduced glomerular filtration rate and renal plasma flow, and it increased renal resistance without an alteration in blood pressure. These changes returned to normal within an hour. It was held that CPZ caused renal vasoconstriction involving both afferent and efferent arterioles. In fact, slightly larger

doses than 3.5 mg of CPZ infused in approximately 2 hours, which decreased blood pressure, reduced urine output to almost zero (61). The observed diuretic effects of CPZ in man are thought to be caused by blockade of the release of ADH. This is supported by findings of Parrish and Levine (216), who detected a decrease in antidiuretic activity in urine of patients during CPZ-induced diuresis. Mefferd *et al.* (182) found an increased urine flow in schizophrenic patients treated for 6 months with approximately 400 mg of CPZ daily, but fluid intake was also increased in these patients. Dilworth *et al.* (83) reported a case of fatal poisoning in a boy of 3 who swallowed 800 mg of CPZ. During treatment of the acute poisoning, marked diuresis occurred. It was suggested that either kidney damage or depression of endogenous release of ADH was the cause of this diabetes insipidus-like effect. Accordingly, CPZ in human subjects induces diuresis rather than antidiuresis, and this may be the result of inhibition of ADH release.

From the results cited, the action of CPZ on pituitary function in man cannot be determined with certainty. Analysis of the action of the drug in patients must necessarily take into account the duration of the treatment, the dosage employed, the measures used to detect the functional state of the gland and the state of the patient at the time activity is determined.

CPZ induces amenorrhea and galactorrhea when administered for several months in relatively high doses. Results suggest that CPZ in female patients under prolonged therapy, as in animals, may induce pseudopregnancy. The effects of CPZ on thyroid function vary considerably and do not permit conclusions about the mode of action of CPZ on thyroid function. The acute administration of CPZ in man, as in animals, seems to increase, while chronic treatment tends to decrease the activity of the pituitary-adrenal system. The activity of this system in response to stress may or may not be reduced depending on the type of stress used. Some evidence points to the adrenal cortex as the site of action of CPZ in blocking pituitary-adrenal activity. CPZ may also affect the posterior pituitary in man by inhibition of the release of ADH since diuresis rather than antidiuresis was observed.

V. CENTRAL EFFECTS OF CHLORPROMAZINE AND THE NERVOUS CONTROL OF THE PITUITARY GLAND

A. Dose-response and structure-activity relationships of chlorpromazine with respect to pituitary activity

CPZ exhibits manifold influences on pituitary function. From the animal studies cited above it may be inferred that a single injection of the drug inhibits the release of TSH, FSH-LH and oxytocin while it stimulates the discharge of ACTH, prolactin, growth hormone and presumably MSH and ADH. Chronic treatment with CPZ leads to blockade of the release of TSH and FSH-LH and stimulation of the release of ACTH and prolactin. Continuous administration of CPZ does not markedly affect the release of oxytocin or ADH, but stress-induced release of oxytocin or ADH may be partially blocked. Pituitary hormone secretion is not necessarily affected by treatment with the phenothazines.

The dose range required to elicit tranquilizing effects lies between 0.5 and 1.5 mg per kg for most animals species (71, 165, 191). These amounts of CPZ do not alter or only slightly alter pituitary function. Failure to inhibit TSH-release (299) or to prevent oxytocin release (54) have been found with doses below 2.5 mg per kg. Similarly, failure to stimulate ACTH release (268) and prolactin release (23) or to elicit significant effects on antidiuresis (158, 273) were found with these amounts of the drug. Doses of 5 mg or more, which exceed those necessary to produce psychodepressant effects, block TSH release (108), ovulation (18), and milk ejection (54) and stimulate ACTH release (164, 268), growth hormone release (187), prolactin release (17, 19, 52), MSH release (140, 258) and antidiuresis (273, 293). Accordingly, CPZ-induced alterations in pituitary activity are not necessarily related to intrinsic psychodepressant properties of the drug. The same may be said for its clinical application. High amounts of the drug given for a considerable time tend to produce endocrine dysfunction. The pituitary-gonad axis seems to be most susceptible of all endocrine functions. Interestingly, this is also the function that disappears first upon damage to the pituitary in animals and in spontaneous pituitary insufficiency in man (104, 171, 223, 261).

Structure-activity relationship studies with respect to endocrine activities of substituted phenothiazines in animal species, however, generally are well correlated with similar relationships on the therapeutic potency of these drugs (14). Increased psychodepressant action in patients results from substitution in the second position with a trifluoromethyl moiety for a chloride substitution and in the tenth position with piperazine structures for the aliphatic side chain (14). In fact, replacing the Cl with CF_3 increases the effect of CPZ on ACTH release (268), prolactin release (21, 146, 284) and MSH release (258), on pituitary MSH depletion (140), on blockade of induced ovulation (232) and, on the mortality rate of offspring (202), but it reduces the effect on ADH release (145, 273). Replacement of the chloride by hydrogen, weakens the blocking effect of the phenothiazine on ACTH release (210), prolactin relase (146), MSH release (258), and ADH release (145, 273). Substitution with SCH_3 however, does not change the antidiuretic potency of the phenothiazine (33) nor the effect on pituitary MSH depletion (140).

Substitution at position 10 may also affect the potency of CPZ on pituitary activity. Replacement of the aliphatic side chain by a piperidine does not materially alter the influence on the pituitary. The stimulatory effect on ACTH release of CPZ and mepazine is about the same (211, 268) and CPZ and thioridazine are also nearly equipotent in producing antidiuresis (33) or pituitary MSH depletion (140). Replacement with a piperazine side chain, however, enhances MSH release, pituitary MSH depletion, and prolactin release (21, 140, 146, 258, 284) while the release of ADH is diminished (145, 280). Accordingly, a trifluoromethyl at position 2 and a piperazine side chain at position 10 except, for the effect on ADH release, enhance the influence of the phenothiazines on the pituitary. This is not in accord with clinical observations comparing psychodepressant effects with the action of phenothiazines on endocrine function. In a review of clinical effects, Ayd (14) stated that the more intense the psychodepressant

effect of the phenothiazine derivative, the less its sedative and hypnotic effect and the less its effect on autonomic and endocrine activity. Among the derivatives discussed, mepazine and CPZ appeared to be more sedative and to exhibit more autonomic and endocrine effects than the piperazine derivatives with a chloride or trifluoromethyl group in the second position, which seem to have more affinity for limbic and extrapyramidal systems. The discrepancy between experimental and clinical studies in this respect may be explained by the fact that in general, relatively more of the drug is administered to animals than to human beings, while the central nervous system of the latter group may be more susceptible to the psychodepressant action of the phenothiazines.

B. Influence of chlorpromazine on midbrain reticular-limbic-hypothalamic connections as a possible locus of action on pituitary activity

The powerful central effects of CPZ make it highly probable that the drug interferes with pituitary function *via* influences exerted at central nervous structures and the abundance of data indicating that brain centers control pituitary function suggests that the action of CPZ concerns those centers which regulate pituitary activity. It is well accepted that the hypothalamus is the final common pathway through which stimuli are funneled to the adenohypophysis (117). Various releasers are produced in this structure (115) and transported *via* the portal vessel system to the adenohypophysis. Presumably the rate of stimulation of the neurons in the hypothalamus that secrete the releasing factors is modified by facilitatory and inhibitory influences exerted by higher brain centers. As Nauta (205) pointed out, the hypothalamus represents a "nodal point" in a series of networks which connect the mesencephalic and rhinencephalic limbic system. By acting on these structures, CPZ may affect pituitary function. Killam (147), who critically reviewed the literature concerning the influence of phenothiazines on the midbrain reticular formation, concluded that evidence that CPZ exerts its tranquilizing effect by a depression of this formation or by depression of incoming information is unconvincing. In a clinically effective dose, which does not affect pituitary function, CPZ also does not depress activity of the midbrain reticular formation. In the dosage in which CPZ in animal experiments alters pituitary function, it elevates the threshold for sensory-induced arousal and also arousal produced by direct stimulation (36, 148, 225). This is shown by findings of Barraclough and Sawyer (18), who showed that in rats a dose of 5 mg of CPZ per kg, which blocks ovulation, also increases EEG arousal threshold to direct stimulation of the midbrain reticular formation. These authors suggested that CPZ, like atropine, morphine and the barbiturates, combines the inhibition of activity in the midbrain reticular formation activity with blockade of the release of pituitary ovulation hormone. In later experiments Sawyer (250) demonstrated that the threshold of the rhinencephalic-hypothalamic EEG afterreaction, which seems to be affected by the concentration of LH in the blood, is more sensitive to CPZ than the threshold of midbrain reticular arousal. It is of interest to note that rhinencephalic-hypothalamic structures are more closely concerned with pituitary-gonadal activity than the midbrain reticular formation (250).

Since similar structures in the brain are involved in the release of the other pituitary hormones, one might expect that the influence of CPZ on the mesencephalic-limbic and on rhinencephalic-limbic structures alters the function of the pituitary gland *via* the hypothalamus.

The fact that release of several of the pituitary hormones is blocked while at the same time that of others is stimulated may be explained by assuming that CPZ stimulates or depresses facilitatory and inhibitory areas in the brain involved in the regulation of pituitary function. For example, electrical stimulation of the anterior hypothalamus stimulates TSH release (6, 45, 118) whereas stimulation of the posterior hypothalamus causes inhibition of thyroid activity in normal and in adrenalectomized rabbits (118). In addition, Anderson *et al.* (4) showed that lesions in the midbrain cause inhibiton of thyroid activity while destruction of preoptic areas leads to its stimulation. In view of these considerations, CPZ may stimulate inhibitory as well as suppress facilitatory areas in the brain to inhibit TSH release. Rhinencephalic and mesencephalic areas exert inhibitory and stimulatory influences on pituitary ACTH release as well. Electrical stimulation of the amygdaloid complex elicits an increase in ACTH release (89, 178, 209, 259, 266). Stimulation of hippocampal areas inhibits ACTH release or prevents stress-induced increase in the discharge of ACTH (90, 178, 276). Destruction of the hippocampus, the septal or anterior hypothalamic areas (29, 154, 170) or the posterior hypothalamus (34, 155) facilitates ACTH release. Local application of CPZ in the mesencephalic reticular formation or in the posterior hypothalamus stimulates ACTH release (30). On the other hand, application of CPZ in the mesencephalic reticular formation, but not in the posterior hypothalamus, blocks pituitary-adrenal activation in response to electrical shock, formalin injection, or immobilization (30). Thus, under appropriate conditions CPZ may exhibit facilitatory and inhibitory influences on ACTH release *via* the same structures in the central nervous system. Lack of knowledge about the action of CPZ on mid-brain reticular-rhinencephalic-hypothalamic connections and of the central organization of the regulation of pituitary function makes it difficult if not impossible to determine the role of higher brain centers on CPZ-induced alterations on pituitary activity. In addition, multiple sites of action of CPZ in the brain must be considered as possible influences that influence pituitary function *via* the hypothalamus. One may therefore assume that, either by depressing afferent input or *via* the centers mentioned above, CPZ is of itself sufficient to cause alteration in pituitary activity.

C. Influence of chlorpromazine on the hypothalamus as a possible locus of action on pituitary activity

Studies indicate that CPZ is evenly distributed in the body and that most of it is concentrated in the brain (245). The hypothalamus seems to contain more than other areas in the brain. De Jaramillo and Guth (132) showed highest concentrations in the hypothalamus, medulla, hippocampus, and midbrain in the dog. Wase *et al.* (292), using ^{35}S-CPZ, found that phenothiazine was widely distributed throughout the areas in the brain, but the hypothalamus exhibited

continual accumulation, indicating specific affinity of CPZ for this brain area. In contrast, Sjöstrand *et al.* (264) found that ^{35}S-CPZ concentrated preferentially in the cerebral cortex, the hippocampus, and the thalamic nuclei. Accumulation studies are doubtful as an index of the site of action of a drug. Yet, other experiments point to the hypothalamus as the locus of action of CPZ. Decsi and Méhes (81) showed that the inhibitory effect of CPZ on oxidative phosphorylation in various parts of the brain of cats and dogs is most marked in the hypothalamus. In this structure, which represents the final common pathway to the pituitary, the nuclei and nerve endings that elaborate the various releasers are situated. If the main action of CPZ is on hypothalamic centers involved in the mechanism of release of pituitary hormones, one has to postulate again that it blocks stimulatory or removes inhibitory influences, or that the regulation of the release of a number of pituitary hormones is reciprocally organized.

Since the area in the hypothalamus that blocks ovulation after a lesion also induces activation of the mammary glands (121, 251) and decreases prolactin content of the anterior pituitary (138), Sawyer and associates proposed that this region of the hypothalamus exerts a reciprocal control over ovulation and lactation; the evidence, however, is conflicting, and other authors maintain the view that there are separate hypothalamic sites for the control of the secretion of FSH-LH and that of prolactin (95, 241, 242). Similar reciprocal relationships seem to exist between other pituitary hormones. A decrease in pituitary-thyroid activity occurs after exposure to a variety of stressful stimuli (44, 117) and in response to the administration of adrenocortical hormones (41, 43). Recently Sakiz and Guillemin (244) showed that TSH release, as induced by thyrotrophin-releasing factor in the rat, is accompanied by a decrease in ACTH release in response to stress, and conversely, when the secretion of ACTH is inhibited by dexamethasone and pentobarbital, the pituitary secretes higher quantities of TSH in response to thyrotrophin-releasing factor. Ducommon *et al.* (85) showed that TSH levels disappear in rats within minutes of minor nonspecific environmental variations and exteroceptive stimuli, which are known to stimulate the release of ACTH also within a few minutes (see for review 103). The same may hold for oxytocin and ADH release. Very strong stimuli to the neurohypophyseal system release both oxytocin and ADH (1, 117, 291). However, emotional stress that stimulates ADH release (285) inhibits the discharge of oxytocin (76), and recent findings of Dingman *et al.* (84) in human subjects indicate a reciprocal relationship in the release mechanism of these 2 octapeptides. This may not always be true. For example, after stalk destruction or pituitary transplantations the anterior pituitary usually secretes prolactin in more-than-normal quantities, while the secretion of other trophic hormones is negligible (see for review 92). Cold environment may release TSH simultaneously with ACTH (5, 153). Several agents that elicit ACTH release, like histamine, fail to promote mammary secretion or pseudopregnancy (186, 277), and the stimulus of suckling or high osmotic pressure releases both oxytocin and ADH (77, 125, 126). If it is accepted for a moment that FSH-LH and prolactin, TSH and ACTH, and oxytocin and ADH are reciprocally released, one may postulate that those areas in the hypothalamus

which regulate the secretion of either of these hormones is at the same time blocked for the release of the counterpart hormones. On the analogy of the stimulation of prolactin secretion by CPZ as the result of blockade of inhibitory structures in the posterior tuberal region of the hypothalamus (138), one may postulate that CPZ blocks hypothalamic structures that normally inhibit the release of ACTH, prolactin or ADH, or stimulate the release of TSH, FSH-LH or oxytocin.

D. Chlorpromazine as a stressor agent

It has been inferred by various workers that CPZ acts as a noxious stimulus and that this explains its effects on pituitary function. Actually, stress, like CPZ, causes ACTH release (103), prolactin release (186), growth hormone release (187), and ADH release (192), while FSH-LH release (186), TSH release (117) and oxytocin release (75) may be blocked. The manifold actions of CPZ in the body, the profound metabolic effects, the marked hemodynamic influences, *etc.* (71), may account for nonspecific activation of the pituitary gland. However, certain aspects of the effect of CPZ on pituitary function argue against this hypothesis. The persistent ACTH release after high doses of the drug (268, 294) is not encountered in common stress situations. Paradoxically, the drug protects against all sorts of stress (15, 26, 56, 62, 136, 137, 197, 198, 215). In addition, induction of continuous blockade of estrous cycles is not related to loss of body weight (74). These observations do not support the hypothesis that CPZ acts as a mere nonspecific stimulus.

E. The antiadrenergic action of chlorpromazine as a possible mode of action on pituitary function

It is widely accepted that catecholamines are formed and stored in the brain. Comparative studies of the distribution of noradrenaline in the brain of different species indicate that the highest levels are localized in the hypothalamus (226, 227, 247, 288, 290). There is evidence of a central antiadrenergic effect of CPZ (123, 176). The effects of CPZ on pituitary function may therefore be explained by its antiadrenergic effects in the hypothalamus.

Blockade of sympathetic activity blocks ovulation (252). In fact, Coppola *et al.* (65) showed that depletion of brain norepinephrine in rats induced ovulatory failure. The monoamine oxidase inhibitor etryptamine (α-ethyltryptamine, Monase) in dogs and rats (105, 254, 282) and other monoamine oxidase inhibitors in man (156) block stress-induced release of ACTH, while stress causes the liberation of catecholamines from the brain (180, 213). However, Smelik (267) showed that rats with reserpine implants in the anterior basal hypothalamus, which deplete catecholamine stores, respond normally to stress with pituitary-adrenal activation. Although Psychoyos (229) argued that CPZ-induced pseudopregnancy is not due to its antiadrenergic or anticholinergic effect since dibenzyline and methantheline both oppose the luteotrophic action of the drug, Coppola *et al.* (66) showed that α-methyl dopa and tetrabenazine, which interfere with catecholamine synthesis, produce pseudopregnancy. Only those drugs which

reduce brain noradrenaline levels can stimulate prolactin release. In this respect it is significant that hypothalamic extracts obtained from rats treated with perphenazine remove the normally operating inhibitory influence of this structure on prolactin release from cultured pituitary tissue (78). Martini (177) showed that introduction of adrenaline into the cerebrospinal fluid of dogs raised TSH titers in plasma within half an hour. However, microinjection of noradrenaline or adrenaline into the hypothalamus in rats did not release TSH (113). Adrenaline can release ADH (64) and block oxytocin release (76). Accordingly, a decrease in sympathetic tone in the hypothalamus may result in removal of inhibitory influences on pituitary secretion of ACTH, prolactin and ADH, and simultaneously block the discharge of TSH, FSH-LH and oxytocin.

The interaction between the autonomic nervous system and pituitary function is not clear. Recent studies from many laboratories using histochemical fluorescence techniques (94) as a measure of detecting the presence, the nature, and the activity of these biogenic amines in the hypothalamus point to an intimate relationship between secretory activity of the pituitary gland and hypothalamic sympathetic activity. Studies as to the effect of psychodepressants on pituitary and on hypothalamic sympathetic activity may be fruitful and eventually demonstrate that the autonomic nervous system is more implicated in the regulation of pituitary function than is realized today.

VI. CONCLUSION

This review surveys the influence of CPZ on pituitary activity. Analysis of the literature indicates that the tranquilizer affects pituitary activity only in amounts that exceed those necessary to induce psychodepressant effects in animal species. In these amounts CPZ appears to block the release of FSH and LH and to stimulate the release of prolactin. It inhibits the discharge of TSH and it stimulates the secretion of ACTH and growth hormone. In addition it seems to increase the release of MSH and ADH and it may block oxytocin-release. The influence of the phenothiazines on pituitary secretion depends on the amount of the drug given, the duration of the treatment and the circumstances, like environmental temperature, under which experiments are performed. The pituitary-gonadal axis of all pituitary functions seems to be most susceptible to the drug in animals and man. Clinically the most frequently observed endocrine dysfunction lies in the pituitary-gonadal axis since amenorrhea and galactorrhea are most commonly seen in female patients treated chronically with relatively high doses of the drug.

The locus of action of the drug with respect to pituitary activity must be sought in the brain, but extremely high doses of CPZ may antagonize the effect of pituitary hormones or the influence of the target hormones on their respective target tissues. In the brain CPZ may facilitate or inhibit structures that are involved in the control of pituitary secretions. Mesencephalic limbic and rhinencephalic limbic structures as well as the hypothalamus, which are known to be affected by CPZ and which are known to be involved in pituitary activity, should be regarded as the site of action of CPZ.

Some of the effects of CPZ on pituitary activity may be explained by its

adrenergic blocking properties. This is based upon the concept that blockade of ovulation, stimulation of prolactin release, as well as MSH release induced by CPZ can be brought about also by depletion of catecholamines in the hypothalamus.

The effect of CPZ and related drugs on pituitary activity is complicated by the manifold actions of the phenothiazines in the body. Profound metabolic influences, hemodynamic effects, and marked disturbances in thermoregulation may affect pituitary secretion in a nonspecific manner. These considerations make it difficult to analyze the site of the action of the drug. This can be overcome if better methods become available to determine pituitary activity. It may then be possible to re-evaluate the effect of the phenothiazines on endocrine activity.

Only if direct measures to determine the respective pituitary hormones in the circulation are employed, and the effect of CPZ is assessed after a single injection or after chronic administration of the drug in various dosages and during various periods of time in animal and man under normothermic and hypothermic conditions, can the influence of CPZ and related drugs on endocrine activity be established with certainty.

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REFERENCES

1. Abrahams, V. C. and Pickford, M.: Simultaneous observations on the rate of urine flow and spontaneous uterine movements in the dog and their relationship to posterior lobe activity. J. Physiol. (London) 126: 329–346, 1954.
2. Alloiteau, J. J.: Action inhibitrice de la chlorpromazine sur le déclenchement de deux types de pseudo-gestation chez la ratte. C. R. Soc. Biol. (Paris) 151: 207–209, 1957.
3. Aleshin, B. V. et Us, L. A.: L'effet de la chlorpromazine sur les fonctions de la structure du lobe antérieur de l'hypophyse dans certaines conditions expérimentales. Probl. Endokrinol. Gormonoter 6: 32–45, 1960.
4. Anderson, E., Bates, R. W., Hawthorne, E., Haymaker, W., Knowlton, K., Rioch, D. M., Spence, W. T. and Wilson, H.: The effects of midbrain and spinal cord transection on endocrine and metabolic functions with postulation of a midbrain hypothalamico-pituitary activating system. Recent Progr. Hormone Res. 13: 21–66, 1957.
5. D'Angelo, S. A.: Central nervous regulation of the secretion and release of thyroid stimulating hormone. In: Advances in Neuroendocrinology, ed. by A. V. Nalbandov, 158–205, Univ. of Illinois Press, Urbana, 1963.
6. D'Angelo, S. A. and Snijder, J.: Electrical stimulation of the hypothalamus and TSH secretion in the rat. Endocrinology 73: 75–80, 1963.
7. Aron, E., Chambon, Y. et Voisin, A.: Action d'un végétativolytique sur réaction hypophyso-surrénalienne du rat blanc. (Application au dosage pratique des substances corticotropes). Bull. Acad. Nat. Méd. 137: 417–420, 1953.
8. Aron, E., Guelfi, J. et Voisin, A.: Étude comparée du comportement hypophyso-surrénalien et thyroïdien du rat blanc traité à la chlorpromazine ou en hypothermie expérimentale. C. R. Soc. Biol. (Paris) 149: 891–896, 1955.
9. Arvay, A., Lampé, L., Kertész, L. and Medveczky, L.: Changes of thyroid function in response to severe nervous stimulation. Acta Endocrinol. (Copenh.) 35: 469–480, 1960.
10. Ashford, A. and Shapero, M.: Effect of chlorpromazine, reserpine, benactyzine and phenobarbitone on the release of corticotrophin in the rat. Brit. J. Pharmacol. 19: 458–463, 1962.
11. Assenmacher, I. and Baylé, J. D.: La sécrétion prolactinique du pigeon en réponse à différents traitements. C. R. Soc. Biol. (Paris) 158: 255–259, 1964.
12. Audibert, A., Forgue, G. et Gage, C.: Influence de la chlorpromazine sur l'activité hypophyso-ovarienne. C.R. Soc. Biol. (Paris) 150: 173–175, 1956.
13. Ayd, F. J.: Prolonged administration of chlorpromazine (thorazine) hydrochloride. J. Amer. Med. Ass. 169: 1296–1301, 1959.
14. Ayd, F. J.: Current status of major tranquilizers. J. Med. Soc. N.J. 57: 4–14, 1960.
15. Azuma, T.: Studies of cold tolerance. Endocrinol. Jap. 8: 50–56, 1961.
16. Bachrach, D., Kőszegi, B., Scultéty, S., Jáki, G. and Korpássy, B.: Effect of autonomic blocking agents on the neurosecretion of the hypothalamus in the albino rat. Acta Physiol. Acad. Sci. Hung. 14: 223–230, 1958.

17. Barraclough, C. A.: Induction of pseudopregnancy in the rat by reserpine and chlorpromasine. Anat. Rec. 127: 262–263, 1957.
18. Barraclough, C. A. and Sawyer, C. H.: Blockade of the release of pituitary ovulating hormone in the rat by chlorpromasine and reserpine: possible mechanisms of action. Endocrinology 61: 341–351, 1957.
19. Barraclough, C. A. and Sawyer, C. H.: Induction of pseudopregnancy in the rat by reserpine and chlorpromasine. Endocrinology 65: 563–571, 1959.
20. Batrinos, M. L. and De Verbizier, J.: Action of chlorpromasine on the endocrine system. Rev. Franç. Étud. Clin. Biol. 7: 87–97, 1962.
21. Ben-David, M., Dikstein, S. and Sulman, F. G.: Production of lactation by non-sedative phenothiasine derivatives. Proc. Soc. Exp. Biol. Med. 118: 265–270, 1965.
22. Bennett, J. L. and Hamilton, L. D.: Effects of chlorpromasine in combination with activating drugs on thyroid function tests. J. Neuropsychiat. 3: 118–122, 1961.
23. Benson, G. K.: Further studies on effects of tranquilising drugs on mammary involution in the rat. Proc. Soc. Exp. Biol. Med. 103: 132–137, 1960.
24. Bernis, R. et Vanek, R.: L'élimination des corticoïdes urinaires réducteurs "totaux" dans le stress chirurgical. Influence de divers modes d'anesthésie. Acta Anaesth. Belg. 2: 116–138, 1958.
25. Betz, D. and Ganong, W. F.: Effect of chlorpromasine on pituitary-adrenal function in the dog. Acta Endocrinol. (Copenh.) 43: 264–270, 1963.
26. de Bias, D. A., Paschkis, K. E. and Cantarow, A.: Effects of chlorpromasine and autonomic nervous system blocking agents in combating heat stress. Amer. J. Physiol. 193: 553–556, 1958.
27. Bloch, S.: Experimentelle Untersuchungen über die hormonalen Grundlagen der Implantation des Säugerkeimes. Experientia 12: 447–448, 1958.
28. Blumberg, A. G.: Effect of chlorpromasine with procyclidine and imipramine on radioactive iodine uptake. J. Clin. Endocrinol. 23: 881–884, 1963.
29. Bohus, B.: The effect of central nervous lesions on pituitary-adrenocortical function in the rat. Acta Physiol. Acad. Sci. Hung. 20: 373–377, 1961.
30. Bohus, B. und Endröczi, E.: Untersuchungen über die Wirkung von Chlorpromasine auf das Hypophysen-Nebennierenrinden System bei Ratten. Endokrinologie 46: 126–133, 1964.
31. Bohus, B. and de Wied, D.: Facilitatory and inhibitory influences of the central nervous system on the pituitary-adrenal axis: A study with chlorpromasine. Abstract First International Symposium on Biorhythms in Clinical and Experimental Endocrinology, pp. 21–22, 1966.
32. Bonaccorsi, A., Garattini, S. and Jori, A.: Studies on the hyperglycaemia induced by chlorpromasine in rats. Brit. J. Pharmacol. 23: 93–100, 1964.
33. Boris, A. and Stevenson, R. H.: Effects of some psychotropic drugs upon urinary water output. Proc. Soc. Exp. Biol. Med. 115: 170–171, 1964.
34. Bouman, P. R., Gaarenstroom, J. H., Smelik, P. G. and de Wied, D.: Hypothalamic lesions and ACTH secretion in rats. Acta Physiol. Pharmacol. Néer. 6: 368–378, 1957.
35. Bourrillon, R., Marcy, R. und Got, R.: Die Wirkung des Chlorpromasins auf die Hypophyso-gonaden Achse. Endokrinologie 37: 285–292, 1959.
36. Bradley, P. B. and Key, B. J.: The effect of drugs on arousal responses produced by electrical stimulation of the reticular formation of the brain. Electroenceph. Clin. Neurophysiol. 10: 97–110, 1958.
37. von Brauchitsch, H.: Endokrinologische Aspekte des Wirkungsmechanismus neuroplegischer Medikamente. Psychopharmacologia 2: 1–21, 1961.
38. Briggs, F. N. and Munson, P. L.: Studies on the mechanism of stimulation of ACTH secretion with the aid of morphine as a blocking agent. Endocrinology 57: 205–219, 1955.
39. Brodie, B. B., Shore, P. A., Silver, S. L. and Pulver, R.: Potentiating action of chlorpromasine and reserpine. Nature (London) 175: 1133–1134, 1955.
40. Brooks, F. P. and Pickford, M.: Conditions under which posterior pituitary hormones increase sodium and potassium excretion by the kidney. In: The Neurohypophysis ed. by H. Heller, pp. 141–153, Butterworths, London, 1957.
41. Brown-Grant, K.: The effect of ACTH and adrenal steroids on thyroid activity, with observations on the adrenal-thyroid relationship. J. Physiol. (London) 131: 58–69, 1956.
42. Brown-Grant, K., Harris, G. W. and Reichlin, S.: The effect of emotional and physical stress on thyroid activity in the rabbit. J. Physiol. (London) 126: 29–40, 1954a.
43. Brown-Grant, K., Harris, G. W. and Reichlin, S.: The influence of the adrenal cortex on thyroid activity in the rabbit. J. Physiol. (London) 126: 41–51, 1954b.
44. Brown-Grant, K. and Pethes, G.: The response of the thyroid gland of the guinea-pig to stress. J. Physiol. (London) 151: 40–50, 1960.
45. Campbell, H. J., George, R. and Harris, G. W.: The acute effects of injection of thyrotrophic hormone or of electrical stimulation of the hypothalmus on thyroid activity. J. Physiol. (London) 152: 527–544, 1960.
46. Castaigne, A.: Action des médications végétativolytiques sur l'hypophyse et sur la surrénale. Presse Méd. 60: 1562, 1952.
47. Chambon, Y.: Action de la chlorpromasine sur l'évolution et l'avenir de la gestation chez la rat. Ann. Endocrinol. (Paris) 16: 912–922, 1955.
48. Chambon, Y.: Action de la chlorpromasine sur le couple hypophysoovarien de la rate gestante. Ann. Endocrinol. (Paris) 18: 80–92, 1957.
49. Chambon, Y.: Effet abortif de la chlorpromasine chez l'animal. Bull. Féd. Soc. Gynéc. Obstét. Franç. 8: 447, 1956.

50. Chambon, Y.: Phénothiazines, ovoimplantation et décidualisation. Bull. Soc. Roy. Belge Gynéc. Obstét. **30**: 573–584, 1960.
51. Charatan, F. B. E. and Bartlett, N. G.: The effect of chlorpromazine (Largactil) on glucose tolerance. J. Ment. Sci. **101**: 351–353, 1955.
52. Chatterjee, A.: Ovarian response to administration of "PMS" (pregnant mare serum) in chlorpromazinized and reserpinized female rats. Naturwissenschaften **52**: 309, 1965a.
53. Chatterjee, A.: Effect of chlorpromazine on the testicular physiology in rats. Experientia **21**: 545–546, 1965b.
54. Chaudhury, R. R.: Release of oxytocin in unanesthetized lactating rats. Brit. J. Pharmacol. **17**: 297–304, 1961.
55. Chaudhury, R. R., Chaudhury, M. R. and Lu, F. C.: Stress-induced block of milk ejection. Brit. J. Pharmacol. **17**: 305–309, 1961.
56. Chedid, L. and Parant, M.: Action antitoxique de la chlorpromazine en l'absence de la médullosurrénale. C.R. Soc. Biol. (Paris) **153**: 263–267, 1959.
57. Cheymol, J., de Leeuw, J. et Oger, J.: Que faut-il penser de l'hypophysectomie pharmacodynamique par la chlorpromazine. C.R. Soc. Biol. (Paris) **148**: 1 13–1216, 1954.
58. Christy, N. P., Longson, D., Horwitz, W. A. and Knight, M. M.: Inhibitory effect of chlorpromazine upon the adrenal cortical response to insulin hypoglycemia in man. J. Clin. Invest. **36**: 543–549, 1957.
59. Ciro, C.: Peripheral nervous system and susceptibility of the tissues for hormonal action: effect of prolactin and chlorpromazine on the peripheral nerves in the mammary gland of the rat. Acta Neuroveg. (Wien) **22**: 333–351, 1961.
60. Cohen, I. M.: Effects of chlorpromazine in psychiatric disorders. Amer. J. Med. Sci. **229**: 355–362, 1955.
61. Cohen, A. M.: Diuretic effect of chlorpromazine in patients with congestive heart failure. Amer. Heart J. **54**: 907–914, 1957.
62. Collins, V. J., Jaffe, R. J. and Zahony, I.: Newer attitudes in management of hemorrhagic shock. The use of chlorpromazine as an adjunct. Surg. Clin. N. Amer. **44**: 173–183, 1964.
63. Colmeiro-Laforet, K.: Galaktorrhoe bei Chlorpromazin-Behandlung. Zentral. Gynäk. **79**: 1569–1573, 1957.
64. O'Connor, W. J. and Verney, E. B.: The effect of increased activity of the sympathetic system in the inhibition of water diuresis by emotional stress. Quart. J. Exp Physiol. **33**: 77–90, 1945.
65. Coppola, J. A., Leonardi, R. G. and Lippmann, W.: Ovulatory failure in rats after treatment with brain norepinephrine depletors. Endocrinology **78**: 225–228, 1966.
66. Coppola, J. A., Leonardi, R. G., Lippmann, W., Perrine, J. W. and Ringler, I.: Induction of pseudopregnancy in rats by depletors of endogenous catecholamines. Endocrinology **77**: 485–490, 1965.
67. Cotui, F. W., Brinitzer, W., Orr, A. and Orr, E.: Effect of chlorpromazine and of reserpine on adrenocortical function. Psychiat. Quart. **34**: 47–61, 1960.
68. Courrier, R. et Baclesse, M.: L'équilibre hormonal au cours de la gestation. Réunion des Endocrinologistes de Langue Française, 3e, Brussels, 1955, 18–20 Juin. Communications présentées à la IIIe Réunion des endocrinologistes de langue françaises. Paris, Masson, 1955.
69. Courrier, R. et Marois, M.: Action de l'hypothermie expérimentale sur la gestation chez le rat. C.R. Soc. Biol. (Paris) **147**: 1922–1924, 1953.
70. Courvoisier, S. et Ducrot, R.: Recherche des effets de la chlorpromazine (4.560 RP) sur la sphère génitale et la croissance. C.R. Soc. Biol. (Paris) **148**: 462–466, 1954.
71. Courvoisier, S., Fournel J., Ducrot, R., Kolsky, M. et Koetschet, P.: Propriétés pharmacodynamiques du chlorhydrate de chloro-3 (diméthylamino-3 propyl)-10 phénothiazine (4.560 RP). Arch. Int. Pharmacodyn. Therap. **92**: 305–361, 1952.
72. Le Coz, A.: Les effets endocriniens d'un traitement à la chlorpromazine à faibles doses. Bull. Féd. Soc. Gynéc. Obstét. (Franç. **9**: 614–616, 1957.
73. Crammer, J. L. and Pover, W. F. R.: Iodine-132 uptakes by the thyroid in psychotics. J. Ment. Sci. **106**: 1371–1376, 1960.
74. Cranston, E. M. and Segal, M. S.: Effect of tranquilizers and other agents on sexual cycle of mice. Proc. Soc. Exp. Biol. Med. **98**: 320–322, 1958.
75. Cross, B. A.: Sympathetico-adrenal inhibition of the neurohypophyseal milk-ejection mechanism. J. Endocrinol. **9**: 7–18, 1953.
76. Cross, B. A.: Neurohormonal mechanisms in emotional inhibition of milk ejection. J. Endocrinol. **12**: 29–37, 1955.
77. Cross, N. A.: Neural control of lactation. In: Milk: The Mammary Gland and Its Secretion, ed. by S. K. Kon and A. T. Cowie, p. 229, Academic Press, New York and London, 1961.
78. Danon, A., Diekstein, S. and Sulman, F. G.: Stimulation of prolactin secretion by perphenazine in pituitary-hypothalamus organ culture. Proc. Soc. Exp. Biol. Med. **114**: 366–368, 1963.
79. Dasgupta, S. R.: The effect of chlorpromazine on antidiuresis produced by 5-hydroxytryptamine (serotonin) in rats. Arch. Int. Pharmacodyn. Therap. **112**: 264–271, 1957.
80. Dasgupta, S. R. and Häusler, H. F.: Effect of chlorpromazine on the induced continuous estrus of ovariectomized rats. Bull. Calcutta Sch. Trop. Med. **3**: 113–114, 1955.
81. Decsi, L. und Méhes, J.: Verschiedene Empfindlichkeit einzelner Hirngebiete gegenüber der entkoppelnden Wirkung von Largactil und Luminal. Acta. Physiol. Acad. Sci. Hung. **14**: 95–98, 1960.
82. Deshaies, G., Richardeau, M. et Dechosal, F.: Chlorpromazine et réserpine en psychiatrie. Ann. méd.-psychol. **1**: 417–476, 1957.
83. Dilworth, N. M., Dugdale, A. E. and Hilton, H. B.: Acute poisoning with chlorpromazine. Lancet **1**: 17–3 138, 1963.

84. Dingman, J. F., Ahmed, A. B. and George, B. C.: Oxytocin secretion in normal and hypopituitary subjects. Abstr. Forty-Eighth Meeting The Endocrine Society, 99, 1966.
85. Ducommon, P., Sakiz, E. and Guillemin, R.: Lability of plasma TSH levels in the rat in response to non-specific exteroceptive stimuli. Proc. Soc. Exp. Biol. Med. **121**: 921–923, 1966.
86. Dundee, J. W., Gray, T. C., Mesham, P. R. and Scott, W. E. B.: Hypothermia with autonomic block in man. Brit. Med. J. **II**: 1237–1243, 1953.
87. Egdahl, R. H. and Richards, J. B.: Effect of chlorpromazine on pituitary ACTH secretion in the dog. Amer. J. Physiol. **185**: 235–238, 1956.
88. Egdahl, R. H., Richards, J. B. and Hume, D. M.: The effect of chlorpromazine on pituitary ACTH secretion in the dog. Research report (Project N M 007-081.22.04) Naval Med. Res. Inst. **13**: 545, 1955.
89. Endrőczi, E.: Contribution to the hypothalamic control of pituitary, ovarian and adrenocortical function. Acta Physiol. Acad. Sci. Hung. **18**: 301–307, 1961.
90. Endrőczi, E., Lissák, K., Bohus, B. and Kovács, S.: The inhibitory influence of archicortical structures on pituitary-adrenal function. Acta Physiol. Acad. Sci. Hung. **16**: 17–22, 1959.
91. Everett, J. W.: Maintenance of pregnancy in rats by hypophyseal autografts. Anat. Rec. **124**: 287–288, 1956.
92. Everett, J. W.: Central neural control of reproductive functions of the adenohypophysis. Physiol. Rev. **44**: 373–431, 1964.
93. Ey, H., Faure, H. et Rappard, P.: Les réactions d'intolérance vis à vis de la chlorpromazine. Encéphale **45**: 790–796, 1956.
94. Falck, B.: Observations on the possibilities of the cellular localisation of monoamines by a fluorescence method. Acta Physiol. Scand. **56**: suppl. 197, 1962.
95. Flerkó, B. und Bárdos, V.: Zwei verschiedene Effekte experimenteller Läsion des Hypothalamus auf die Gonaden. Acta Neuroveg. (Wien) **20**: 248–262, 1959.
96. Földes, J., Nagy, J., Kertai, P. and Takacs, E.: Effect of chlorpromazine on thyroid activity. Acta Med. Acad. Sci. Hung. **14**: 371–378, 1959.
97. Foote, R. H. and Gray, L. C.: Effect of promazine hydrochloride and chlorpromazine hydrochloride on motility and fertility of bovine semen. J. Dairy Sci. **43**: 1499–1504, 1960.
98. Foote, R. H. and Gray, L. C.: Effect of tranquilizers on libido sperm production, and *in vitro* sperm survival in dogs. Proc. Soc. Exp. Biol. Med. **114**: 396–398, 1963.
99. Fotherby, K., Forrest, A. D. and Laverty, S. G.: The effect of chlorpromazine on adrenocortical function. Acta Endocrinol. (Copenh.) **32**: 425–436, 1959.
100. Friedell, M. T.: Effect of tranquilizing agents on radioactive iodine uptake in the thyroid gland. J. Amer. Med. Ass. **167**: 983–984, 1958.
101. Gäde, E. B. und Heinrich, K.: Klinische Beobachtungen bei Megaphenbehandlung in der Psychiatrie. Nervenarzt **26**: 49–54, 1955.
102. Gale, C. C., Taleisnik, S., Friedman, H. M. and McCann, S. M.: Hormonal basis for impairment in milk synthesis and milk ejection following hypothalamic lesions. J. Endocrinol. **23**: 303–316, 1961.
103. Ganong, W. F.: The central nervous system and the synthesis and release of adrenocorticotropic hormone. In: Advances in Neuroendocrinology, ed. by A. V. Nalbandov, pp. 92–149, Univ. of Illinois Press, Urbana, 1963.
104. Ganong, W. F. and Hume, D. M.: The effect of graded hypophysectomy on thyroid, gonadal and adrenocortical function in the dog. Endocrinology **59**: 293–301, 1956.
105. Ganong, W. F., Wise, B. L., Shackleford, R., Boryczka, A. T. and Zipf, B.: Site at which α-ethyltryptamine acts to inhibit the secretion of ACTH. Endocrinology **76**: 526–530, 1965.
106. Gaulhofer, W. K., Schaank, J. R. H. and Vali, A.: Galactorroe veroorzaakt door chloorpromazine. Ned. T. Geneesk. **101**: 264–266, 1957.
107. Gaunt, R., Chart, J. J. and Renzi, A. A.: Interactions of drugs with endocrines. Annu. Rev. Pharmacol. **3**: 109–128, 1963.
108. George, R. and Lomax, P.: The effects of morphine, chlorpromazine and reserpine on pituitary-thyroid activity in rats. J. Pharmacol. Exp. Therap. **150**: 129–134, 1965.
109. Georges, G. and Cahn, J.: Couple hypophyso-surrénalien et hibernation. Anesth. Analg. **10**: 409–419, 1953.
110. Gillet, E.: Effects of chlorpromazine and D-lysergic acid diethylamide on sex behavior of male rats. Proc. Soc. Exp. Biol. Med. **103**: 392–394, 1960.
111. Gitsch, E.: Evaluation of combined implantation of ovary and uterus in the spleen of castrate rats as a measure of gonadotropic activity. Acta Endocrinol. (Copenh.) **30**: 1–21, 1959.
112. Gold, E. M., DiRaimondo, V. C., Kent, J. R. and Forsham, P. H.: Comparative effects of certain non-narcotic central nervous system analgesics and muscle relaxants on the pituitary adrenocortical system. Ann. N.Y. Acad. Sci. **86**: 178–190, 1960.
113. Greer, M. A., Yamada, T. and Iino, S.: The participation of the nervous system in the control of thyroid function. Ann. N.Y. Acad. Sci. **86**: 667–675, 1960.
114. Grönroos, M., Kalliomäki, J. L., Keyriläinen, T. O. and Marianen, P.: Effects of reserpine and chlorpromazine on the mammary glands of the rat. Acta Endocr. (Copenh.) **31**: 154–160, 1959.
115. Guillemin, R.: Hypothalamic factors releasing pituitary hormones. Recent Progr. Hormone Res. **20**: 89–130, 1964.
116. Hamburger, Chr.: Substitution of hypophysectomy by the administration of chlorpromazine in the assay of corticotrophin. Acta Endocr. (Copenh.) **20**: 383–390, 1955.
117. Harris, G. W.: The Neural Control of the Pituitary. Arnold, London, 1955.
118. Harris, G. W. and Woods, J. W.: The effect of electrical stimulation of the hypothalamus or pituitary gland on thyroid activity. J. Physiol. (London) **143**: 246–274, 1958.

119. HARWOOD, C.Th. AND MASON, J. W.: Effects of tranquilizing drugs on the anterior pituitary-ACTH mechanism. Endocrinology 60: 239–246, 1957.
120. HASSELBLATT, A. UND SCHUSTER, R.: Wirkung von Megaphen und Veronal auf die Rastinonhypoglykämie. Klin. Wochensch. 36: 814–819, 1958.
121. HAUN, C. K. AND SAWYER, C. H.: Initiation of lactation in rabbits following placement of hypothalamic lesions. Endocrinology 67: 270–272, 1960.
122. HAUSER, G. A., KRESSIG, R., KELLER, M., WENNER, R., BATTEGAY, R. UND BERGER, J.: Die Largactil-(Megaphen)-Amenorrhoe. Geburtsh. u. Frauenheilk. 18: 637–639, 1958.
123. HIEBEL, G., BONVALLET, M. ET DELL, P.: Action de la chlorpromazine (Largactil) au niveau du système nerveux central. Sem. Hôp. Paris 30: 2346–2354, 1954.
124. HOFFMAN, R. A.: Influence of the adrenal gland on hypothermic response of the rat to chlorpromazine, reserpine and serotonin. Amer. J. Physiol. 196: 876–880, 1959.
125. HOLLAND, R. C., CROSS, B. A. AND SAWYER, C. H.: Effects of intracarotid injections of hypertonic solutions on the neurohypophyseal milk-ejection mechanism. Amer. J. Physiol. 196: 791–795, 1959a.
126. HOLLAND, R. C., CROSS, B. A. AND SAWYER, C. H.: EEG correlates of osmotic activation of the neurohypophyseal milk-ejection mechanism. Amer. J. Physiol. 196: 796–802, 1959b.
127. HOLZBAUER, M. AND VOGT, M.: The action of chlorpromazine on diencephalic sympathetic activity and on the release of adrenocorticotrophic hormone. Brit. J. Pharmacol. 9: 402–407, 1954.
128. HORMIA, A., KANGAS, S. AND HORMIA, M.: The modifying effect of hydrocortisonacetate on the chlorpromazine caused changes of the adrenal cortex in the white rat. Ann. Med. Exp. Biol. Fenn. 36: 394–402, 1958.
129. HUNTER, A. R.: Chlorpromazine as an aid to cooling in a thyroid crisis. Lancet II: 173–174, 1955.
130. JACOBSON, L. E.: Differential effects of chlorpromazine and pitressin on water balance in albino rats. J. Amer. Osteopath. Ass. 64: 957, 1965.
131. JAGIELLO, G. M.: Chlorpromazine as a goitrogen. Fedn. Proc. Fedn. Amer. Socs. Exp. Biol. 18: 75, 1959.
132. DE JARAMILLO, G. A. V. AND GUTH, P. S.: A study of the localization of phenothiazines in dog brain. Biochem. Pharmacol. 12: 525–532, 1963.
133. JARRETT, R. J.: Some endocrine effects of two phenothiazine derivatives, chlorpromazine and perphenazine in the female mouse. Brit. J. Pharmacol. 20: 497–506, 1963.
134. JONES, I. H. AND MEADE, T. W.: Hypothermia following chlorpromazine therapy in myxoedematous patients. Geront. Clin. (Basel) 6: 252–256, 1964.
135. JORI, A., BERNARDI, D. AND GARATTINI, S.: Chlorpromazine and glucose metabolism. Int. J. Neuropharmacol. 3: 553–558, 1964.
136. JUSZKIEWICZ, T.: Effects of chlorpromazine, reserpine and ascorbic acid in resisting heat stress in rats. Amer. J. Vet. Res. 22: 537–543, 1961.
137. JUSZKIEWICZ, T. AND MEYER JONES, L.: Effects of chlorpromazine and ascorbic acid in rats during simulated transportation conditions at normal and high temperatures. Amer. J. Vet. Res. 22: 544–548, 1961.
138. KANEMATSU, S., HILLIARD, J. AND SAWYER, C. H.: Effect of reserpine on pituitary prolactin content and its hypothalamic site of action in the rabbit. Acta Endocrinol. (Copenh.) 44: 467–474, 1963.
139. KASTIN, A. J. AND ROSS, G. T.: Melanocyte-stimulating hormone activity in pituitaries of frogs with hypothalamic lesions. Endocrinology 77: 45–48, 1965.
140. KASTIN, A. J. AND SCHALLY, A. V.: MSH activity in pituitary glands of rats treated with tranquilizing drugs. Endocrinology 79: 1018–1020, 1966.
141. KEHL, R., AUDIBERT, A. ET FORGUE, G.: Quelques influences du largactil sur le système endocrinien. Bull. Féd. Soc. Gynéc. Obstét. Franç. 8: 78–80, 1956b.
142. KEHL, R., AUDIBERT, A., GAGE, C. ET AMARGER, J.: Influence expérimentale de la réserpine sur l'activité hypophyso-génitale. C.R. Soc. Biol. (Paris) 150: 981–983, 1956a.
143. KEUSKAMP, J. W., KAUFMANN, G. W. AND DE WIED, D.: The effect of Nembutal on the eosinopenic response to several compounds. Acta Endocrinol. (Copenh.) 24: 303–306, 1957.
144. KHAN, M. Y. AND BERNSTORF, E. C.: Effect of chlorpromazine and reserpine upon pituitary function. Exp. Med. Surg. 22: 363–378, 1964.
145. KHAZAN, N., BEN-DAVID, M. AND SULMAN, F. G.: Antidiuretic hormone (ADH)-like effect of tranquilizers in amphibians. Proc. Soc. Exp. Biol. Med. 112: 490–494, 1963.
146. KHAZAN, N., PRIMO, CH., DANON, A., ASSAEL, M., SULMAN, F. G. AND WINNIK, H. Z.: The mammotropic effect of tranquilizing drugs. Arch. Int. Pharmacodyn. Thérap. 136: 291–305, 1962.
147. KILLAM, E. K.: Drug action on the brain-stem reticular formation. Pharmacol. Rev. 14: 175–223, 1962.
148. KILLAM, E. K. AND KILLAM, K. F.: The influence of drugs on central afferent pathways. In: Brain Mechanisms and Drug Action, ed. by W. Fields, pp. 71–94, Charles C Thomas, Springfield, Ill., 1957.
149. KINBERGER, B., LASSENIUS, B. AND OSTERMAN, E.: Effects of chlorpromazine on the pituitary adrenocortical system in man. Nord. Med. 55: 723–727, 1956.
150. KITAY, J. I., HOLUB, D. A. AND JAILER, J. W.: "Inhibition" of pituitary ACTH release after administration of reserpine or epinephrine. Endocrinology 65: 548–554, 1959.
151. KIVALO, E., RINNE, U. K. AND MARJANEN, P.: Diuretic effect of chlorpromazine, with special reference to hypothalamic neurosecretory substance. Ann. Med. Exp. Biol. Fenn. 36: 185–190, 1958.
152. KLEPPING, J., MICHEL, R., TRUCHOT, R., BOUCQUEMONT, J. AND TRON-LOISEL, H.: Influence of adrenaline and various sympathomimetic drugs on ascorbic acid and cholesterol of the adrenals of the rat. C.R. Soc. Biol. (Paris) 155: 57–61, 1961.
153. KNIGGE, K. M.: Neuroendocrine mechanisms influencing ACTH and TSH secretion and their role in cold acclimation. Fedn. Proc. Fedn. Amer. Socs. Exp. Biol. 19: 45–51, 1960.

154. KNIGGE, K. M. AND HAYS, M.: Evidence of inhibitive role of hippocampus in neural regulation of ACTH release. Proc. Soc. Exp. Biol. Med. 114: 67–69, 1963.
155. KNIGGE, K. M., PENROD, C. H. AND SCHINDLER, W. J.: *In vitro* and *in vivo* adrenal corticosteroid secretion following stress. Amer. J. Physiol. 196: 579–582, 1959.
156. KOTHARI, N. J., SAUNDERS, J. C. AND KLINE, N. S.: Effect of phenothiazines and hydrazines on pituitary-adrenal-cortical response. Psychopharmacologia 2: 22–26, 1961.
157. KOVÁCS, K., HORVÁTH, E., KOVÁCS, B., KOVÁCS, G. S. AND PETRI, G.: The influence of chlorpromazine on the changes of the adrenal cortex caused by hypertonic saline in rats. Arch. Int. Pharmacodyn. Thérap. 108: 170–179, 1956.
158. KOVÁCS, K., KOVÁCS, G. S., KOVÁCS, B. M. AND PETRI, G.: The effect of chlorpromazine on the activity of the antidiuretic hormone. Arch. Int. Pharmacodyn. Thérap. 109: 1–7, 1957.
159. KRAIS, W., LEHR, H. UND RIESS, W.: Beeinflusst die Megaphenbehandlung trächtiger und säugender Ratten die Entwicklung der Jungen? (Ein tierexperimenteller Beitrag zur Megaphenbehandlung der Hyperemesis gravidarum). Arch. Gynäk. 185: 248–250, 1954.
160. KRULICH, L. AND MCCANN, S. M.: Influence of stress on the growth hormone (GH) content of the pituitary of the rat. Proc. Soc. Exp. Biol. Med. 122: 612–616, 1966.
161. KSYCKI, S. M. J. AND LOCKETT, S. M. C.: Effects of chlorpromazine on radioiodine uptake and metabolism in C-57 brown mice. Life Sci. 4: 1877–1886, 1965.
162. KULCSAR, S., POLISHUK, W. ET RUBIN, L.: Aspects endocriniens du traitement à la chlorpromazine. Presse Méd. 65: 1288–1290, 1957.
163. LABORIT, H. ET HUGUENARD, P.: L'hibernation artificielle par moyens pharmacodynamiques et physiques. Presse Méd. 64: 1329, 1951.
164. LAMMERS, J. G. R.: De invloed van chlorpromazine op het hypophyse-bijniersysteem van de rat. Thesis, Utrecht, 1965.
165. LAMMERS, J. G. R. AND DE WIED, D.: The effect of chlorpromazine on exploratory and avoidance behaviour and on pituitary-adrenal activity in rats. Acta Physiol. Pharmacol. Néer. 12: 169–170, 1963.
166. LAMMERS, J. G. R. AND DE WIED, D.: The blocking action of chlorpromazine on stress-induced pituitary-adrenal activity in nembutalized rats. Acta Physiol. Pharmacol. Néer. 13: 103, 1964.
167. LANGER, M. AND GNUDI, A.: Sviluppo della ghiandola mammaria e secrezione lattea in ratte impuberi trattare con chlorpromazine. Folia endocrinol. (Pisa) 14: 705–716, 1961.
168. LESSIN, A. W. ET PARKES, M. W.: The relation between sedation and body temperature in the mouse. Brit. J. Pharmacol. 12: 245–250, 1957.
169. LEWIN, D., ROBEY, M. ET SIMONNET, H.: Effets du 4.560 R.P. sur les modifications cycliques de l'épithélium vaginal de la rate. Bull. Féd. Soc. Gynéc. Obstét. Franç. 7: 129–134, 1955.
170. LISSÁK, K. AND ENDRŐCZI, E.: Neuroendocrine interrelationships and behavioural processes. In: Major Problems in Neuroendocrinology, ed. by E. Bajusz and G. Jasmin, pp. 1–16, S. Karger, Basle, 1964.
171. LLOYD, C. W.: Central nervous system regulation of endocrine function in the human. In: Advances in Neuroendocrinology, ed. A. V. Nalbandov, pp. 460–500, Univ. of Illinois Press, Urbana, 1963.
172. LŐVEI, E., MASSZI, F. UND TILL, G.: Erfahrungen mit Chlorpromazin bei Hyper- und Hypothyreose. Wien Med. Wochensch. 109: 151–152, 1959.
173. MAHFOUZ, M. AND EZZ, E. A.: The effect of reserpine and chlorpromazine on the response of the rat to acute stress. J. Pharmacol. Exp. Therap. 123: 39–42, 1958.
174. MAROCCO, F. AND BRENA, S.: Variazione della captazione tiroidea della I^{131} nella cavia per azione de l'4560 RP. Minerva Anesth. 12: 332–334, 1953.
175. MARSHALL, W. K. AND LEIBERMAN, D. M.: A rare complication of chlorpromazine treatment. Lancet I: 162, 1956.
176. MARTIN, W. R., DE MAAR, E. W. J. AND UNNA, K. R.: The action of chlorpromazine and related phenothiazines on the EEG and its activation. J. Pharmacol. Exp. Therap. 122: 343–358, 1958.
177. MARTINI, L.: Sui rapporti tra ipofisi e tiroide; l'ormone tireotropico, p. 223, Edizioni del premio Ganassini, Milano, 1956.
178. MASON, J. W.: Plasma 17-hydroxycorticosteroid response to hypothalamic stimulation in the conscious rhesus monkey. Endocrinology 63: 403–411, 1958.
179. MAYER, S. W., KELLY, F. H. AND MORTON, M. E.: The direct anti-thyroid action of reserpine chlorpromazine and other drugs. J. Pharmacol. Exp. Therap. 117: 197–201, 1956.
180. MAYNERT, E. W. AND LEVI, R.: Stress-induced release of brain norepinephrine and its inhibition by drugs. J. Pharmacol. Exp. Therap. 143: 90–95, 1964.
181. MCCANN, S. M., FRUIT, A. AND FULFORD, B. D.: Studies on the loci of action of cortical hormones in inhibiting the release of adrenocorticotrophin. Endocrinology 63: 29–42, 1958.
182. MEFFERD, R. B. JR., LABROSSE, E. H., GAWIENOWSKI, A. M. AND WILLIAMS, R. J.: Influence of chlorpromazine on certain biochemical variables of chronic male schizophrenics. J. Nerv. Ment. Dis. 127: 167–179, 1958.
183. MEIDINGER, F.: Action comparée sur l'hypophyse d'antihistaminiques, de neuroplégiques et d'anti-inflammatoires. C.R. Soc. Biol. (Paris) 148: 1086–1090, 1954.
184. MEIER, R., BRÜNI, C. ET TRIPOD, J.: Différenciation pharmacodynamique de l'aprésoline, du serpasil et de la chlorpromazine lors de leur action sur la rétention hydrique du rat. Arch. Int. Pharmacodyn. Thérap. 104: 137–146, 1955.
185. MEITES, J., KAHN, R. H. AND NICOLL, C. S.: Prolactin production by rat pituitary explants *in vitro*. Proc. Soc. Exp. Biol. Med. 108: 440–443, 1961.

186. MEITES, J., NICOLL, C. S. AND TALWALKER, P. K.: The central nervous system and the secretion and release of prolactin. In: Advances in Neuroendocrinology, ed. by A. V. Nalbandov, pp. 238–277, University of Illinois Press, Urbana, 1963.
187. MEYER, V. AND KNOBIL, E.: Growth hormone secretion in the unanesthetized Rhesus monkey in response to noxious stimuli. Endocrinology, 1967, **80**: 163–171, 1967.
188. MILCOU, S. M., NEGOESCOU, I., PETRESCOU, C., LUPULESCO, A. ET COCOU, F.: Contribution à l'étude de l'action de la chlorpromazine sur la glande thyroïde. Ann. Endocrinol. **18**: 902–915, 1957.
189. MILCOU, S. M., NEGOESCOU, I., RADIAN, N., BOJINESCOU, A., PETRESCOU, C., COCOU, F. AND STANCOU, H.: The effect of chlorphenothiazine (chlorpromazine) on the concentration of radioiodine (I^{131}) in the thyroid of the albino rat. Proceeding International Conference Peaceful Uses of Atomic Energy Geneva **10**: 331–333, 1955.
190. MILIN, R. AND STERN, P.: Effect of chlorpromazine on hyperthyroidism in hares. Med. Pregl. **8**: 280–285, 1955.
191. MILLER, R. E., MURPHY, J. V. AND MIRSKY, I. A.: The effect of chlorpromazine on fear-motivated behavior in rats. J. Pharmacol. Exp. Therap. **120**: 379–387, 1957.
192. MIRSKY, I. A., STEIN, M. AND PAULISCH, G.: The secretion of an antidiuretic substance into the circulation of rats exposed to noxious stimuli. Endocrinology **54**: 491–505, 1954.
193. MISHINSKY, J., LAITOS, E. K. AND SULMAN, F. G.: Initiation of lactation by hypothalamic implantation of perphenazine. Endocrinology **78**: 919–922, 1966.
194. MOSES, A. M.: Adrenal-neurohypophysial relationships in the dehydrated rat. Endocrinology **73**: 230–236, 1963.
195. MOSES, A. M.: Inhibition of vasopressin release in rats by chlorpromazine and reserpine. Endocrinology **74**: 889–893, 1964.
196. MOYER, J. H., KENT, B., KNIGHT, R., MORRIS, G., HUGGINS, R. AND HANDLEY, C. A.: Laboratory and clinical observations on chlorpromazine (SKF-2601-A)-hemodynamic and toxicological studies. Amer. J. Med. Sci. **227**: 283–290, 1954.
197. MRAZ, M. AND TRINER, L.: The adrenergic reaction in shock and its pharmacological control. Arch. Int. Pharmacodyn. Thérap. **152**: 267–276, 1964a.
198. MRAZ, M. AND TRINER, L.: The influence of various substances on metabolism and resistance of traumatized rats. Arch. Int. Pharmacodyn. Thérap. **152**: 366–378, 1964b.
199. MUELLER, R., BRAUSCH, C. C., HIRSCH, E. Z., BENUA, R. S. AND DOBLINS, B. M.: Uptake of radioactive iodine in the thyroid of patients with impaired liver function. J. Clin. Endocrinol. **14**: 1287–1299, 1954.
200. MÜLLER, E. E., SAITO, T., KASTIN, A. J. AND PECILE, A.: Blockade of release of growth hormone (GH) by drugs acting on the central nervous system. Abstracts Forty-Eighth Meeting The Endocrine Society, p. 28, 1966.
201. MUNSON, P. L.: Pharmacology of neuroendocrine blocking agents. In: Advances in Neuroendocrinology, ed. by A. V. Nalbandov, pp. 427–444, Univ. of Illinois Press, Urbana, 1963.
202. MURPHREE, O. D., MONROE, B. L. AND SEAGER, L. D.: Survival of offspring of rats administered phenothiazines during pregnancy. J. Neuropsychiat. **3**: 295–297, 1962.
203. NAGATA, G.: Influence of chlorpromazine upon the pituitary function, especially corticotropine and gonadotropin secretion. A. R. Shionogi Res. Lab. **7**: 71–86, 1957.
204. NASMYTH, P. A.: The effect of chlorpromazine on adrenocortical activity in stress. Brit. J. Pharmacol. **10**: 336–339, 1955.
205. NAUTA, W. J. H.: Central nervous organization and the endocrine motor system. In: Advances in Neuroendocrinology, ed. by A. V. Nalbandov, pp. 5–21, Univ. of Illinois Press, Urbana, 1963.
206. NEWMAN, S. AND FISH, V. J.: The influence of tranquilizing drugs on results of thyroid function studies. J. Clin. Endocrinol. **18**: 1296–1301, 1958.
207. NORMAN, D. AND HIESTRAND, W. A.: Glycemic effects of chlorpromazine in the mouse, hamster and rat. Proc. Soc. Exp. Biol. Med. **90**: 89–91, 1955.
208. OHLER, E. A. AND SEVY, R. W.: Inhibition of stress induced adrenal ascorbic acid depletion by morphine, dibenzyline and adrenal cortex extract. Endocrinology **59**: 347–355, 1956.
209. OKINAKA, S., IBAYASHI, H., MOTOHASHI, K., FUJITA, T., YOSHIDA, S., OHSAWA, N. AND MURAKAWA, S.: Regulation of the pituitary-adrenocortical function through the limbic system and reticular formation. Acta Endocrinol. (Copenh.) **35** (suppl. 51) 43–44, 1960.
210. OLLING, CH. C. J. AND DE WIED, D.: Inhibition of the release of corticotrophin from the hypophysis by chlorpromazine. Acta Endocrinol. (Copenh.) **22**: 283–292, 1956.
211. OLLING, CH. C. J. AND DE WIED, D.: The influence of pacatal on the corticotrophin-releasing activity of the hypophysis. Acta Endocrinol. (Copenh.) **28**: 428–434, 1958.
212. ORDY, J. M., LATANICK, A., JOHNSON, R. AND MASSOPUST, L. C., JR.: Chlorpromazine effects on pregnancy and offspring in mice. Proc. Soc. Exp. Biol. Med. **113**: 833–836, 1963.
213. ORDY, J. M., SAMORAJSKI, T. AND SCHOEDER, D.: Concurrent changes in hypothalamic and cardiac catecholamine levels after anesthetics tranquilizers and stress in a subhuman primate. J. Pharmacol. Exp. Therap. **152**: 444–457, 1966.
214. PANTIĆ, V., TEŠIĆ, D. AND JOVANOVIĆ, M.: The influence of chlorpromazine on the thyroid of the rat. Acta Anat., Abstr. **46**: 176–177, 1961.
215. PARANT, M. AND CHEDID, L.: Protective effect of chlorpromazine against endotoxin-induced abortion. Proc. Soc. Exp. Biol. Med. **116**: 906–909, 1964.
216. PARRISH, A. E. AND LEVINE, E. H.: Chlorpromazine-induced diuresis. J. Lab. Clin. Med. **48**: 264–269, 1956.
217. PASTEELS, J. L.: Premiers résultats de culture combinée *in vitro* d'hypophyse et d'hypothalamus dans le but d'en apprécier la sécrétion de prolactin. C.R. Acad. Sci. (Paris) **253**: 3074–3075, 1961.
218. PASTEELS, J. L.: Administrations d'extraits hypothalamiques à l'hypophyse de rat *in vitro*, dans le but d'en contrôler la sécrétion de prolactin. C.R. Acad. Sci. (Paris) **254**: 2664–2666, 1962.

219. Pecile, A. and Müller, E.: Suppressive action of corticosteroids on the secretion of growth hormone. J. Endocrinol. 36: 401–408, 1966.
220. Van Peenen, P. F. D. and Way, L. E.: The effect of certain central nervous system depressants on pituitary-adrenal activating agents. J. Pharmacol. Exp. Therap. 120: 261–267, 1957.
221. Pekkarinen, A., Niemelä, N., Stanienie, E. and Tala, E.: The neurogenic influence of dogs and cats on the corticosteroid content in rat plasma and the excretion of corticosteroids in guinea pig. Abstracts International Congress on Hormonal Steroids, 1962, Exc. Med. Congress Ser. No. 51, 167, 1962.
222. Perry, W. F. and Hughes, J. F. S.: The urinary excretion and thyroid uptake of iodine in renal disease. J. Clin. Invest. 3: 457–463, 1952.
223. Peters, J. P., German, W. J., Mann, E. B. and Welt, L. G.: In man progressive pituitary disease is usually associated first with symptoms of gonaded depression than with thyroid and adrenocortical function of gonad, thyroid and adrenals in hypopituitaries. Metabolism 3: 118–137, 1954.
224. Polishuk, W. Z. and Kulcsar, S.: Effects of chlorpromazine on pituitary function. J. Clin. Endocrinol. 16: 292–293, 1956.
225. Preston, J. B.: Effects of chlorpromazine on the central nervous system of the cat: a possible neural basis for action. J. Pharmacol. Exp. Therap. 118: 100–115, 1956.
226. Pscheidt, G. R. and Himwich, H. E.: Reserpine, monoamine oxidase inhibitors and distribution of biogenic amines in monkey brain. Biochem. Pharmacol. 12: 65–71, 1963.
227. Pscheidt, G. R., Molpurgo, C. and Himwich, H. E.: Studies on norepinephrine and 5-hydroxytryptamine in various species. In: Comparative Neurochemistry, ed. by D. Richter, pp. 401–413, Pergamon Press, New York, 1964.
228. Psychoyos, A.: Retard de la nidation de l'oeuf chez la ratte à l'aide de la chlorpromazine; action de l'oestrogène. C.R. Acad. Sci. (Paris) 248: 3216–3218, 1959.
229. Psychoyos, A.: Considérations sur les rapports de la chlorpromazine et de la lutéotrophine hypophysaire. C.R. Soc. Biol. (Paris) 152: 918–920, 1958.
230. Psychoyos, A.: Nouvelle contribution à l'étude de la nidation de l'oeuf chez la ratte. C.R. Acad. Sci. (Paris) 251: 3073–3075, 1960.
231. Psychoyos, A.: A study of the hormonal requirements for ovum implantation in the rat, by means of delayed nidation-inducing substances (chlorpromazine, trifluoperazine). J. Endocrinol. 27: 337–343, 1963.
232. Pushottam, W., Mason, M. M. and Pincus, G.: Induced ovulation in the mouse and the measurement of its inhibition. Fertil. Steril. 12: 346–352, 1961.
233. Py, O. and Mathieu, P.: Galactorrhée et troubles du cycle menstruel au cours de traitements neuroleptiques. Presse Méd. 68: 765–766, 1960.
234. Radde, I. C. and Kalow, W.: Some aspects of thyroid function in rats after feeding of levomepromazine. J. Pharmacol. Exp. Therap. 130: 436–443, 1960.
235. Reichlin, S., Koussa, M. G. and Witt, F. W.: Effect of prolonged sleep therapy and of chlorpromazine on plasma protein-bound iodine concentration and plasma thyroxin turnover. J. Clin. Endocrinol. 19: 692–699, 1959.
236. Reiss, M.: Endocrine concomitants of certain physical psychiatric treatments. J. Clin. Exp. Psychopath. 17: 254–262, 1956.
237. Reiss, M.: Influence of chlorpromazine on endocrine function. In: Psychoendocrinology, pp. 182–197, Grune and Stratton, New York, 1958.
238. Řežábek, K. and Votava, Z.: The action of some antihistaminics and neuroplegics on the release of ACTH in surgical stress in rats. Arch. Int. Pharmacodyn. Thérap. 108: 279–288, 1956.
239. Robinson, B.: Breast changes in the male and female with chlorpromazine or reserpine therapy. Med. J. Aust. 44: 239–241, 1957.
240. Roizin, L., True, C. and Knight, M.: Structural effects of tranquilizers. Res. Publs. Ass. Res. Nerv. Ment. Dis. 37: 285–324, 1959.
241. Rothchild, I.: The corpus luteum-pituitary relationship: the association between the cause of luteotrophin secretion and the cause of follicular quiescence during lactation; the basis for a tentative theory of the corpus luteum-pituitary relationship in the rat. Endocrinology 67: 9–41, 1960.
242. Rothchild, I.: Corpus luteum-pituitary relationship. The effect of progesterone on the folliculotropic potency of the pituitary in the rat. Endocrinology 70: 303–313, 1962.
243. Ryall, R. W.: Some actions of chlorpromazine. Brit. J. Pharmacol. 11: 339–345, 1956.
244. Sakiz, E. and Guillemin, R.: Inverse effects of purified hypothalamic TRF on the acute secretion of TSH and ACTH. Endocrinology 77: 797–801, 1965.
245. Salzman, N. P. and Brodie, B. D.: Physiological disposition and fate of chlorpromazine and a method for its estimation in biological material. J. Pharmacol. Exp. Therap. 118: 46–54, 1956.
246. Samel, M.: Blocking of the thyrotrophic hormone secretion by morphine and chlorpromazine in rats. Arch. Int. Pharmacodyn. Thérap. 117: 151–157, 1958.
247. Samojarski, T. and Marks, B. H.: Localization of tritiated norepinephrine in mouse brain. J. Histochem. Cytochem. 10: 392–399, 1962.
248. Sapeika, N.: The effect of chlorpromazine, iproniazid and chloroquine on adrenal ascorbic acid in the rat. Arch. Int. Pharmacodyn. 122: 196–200, 1959.
249. Sasaki, Sh.: Studies on the central regulation of the pituitary-adrenocortical system. Acta med. biol. 11: 185–212, 1963.
250. Sawyer, C. H.: Mechanism by which drugs and hormones activate and block release of pituitary gonadotropins. Proceedings First International Pharmacological Meeting 1: 27–46, 1963.

251. Sawyer, C. H., Haun, C. K., Hilliard, J., Radford, H. M. and Kanematsu, S.: Further evidence for the identity of hypothalamic areas controlling ovulation and lactation in the rabbit. Endocrinology 73: 338–344, 1963.
252. Sawyer, C. H., Markee, J. E. and Hollinshead, W. H.: Inhibition of ovulation in the rabbit by the adrenergic-blocking agent dibenamine. Endocrinology 41: 395–402, 1947.
253. Sayers, G.: The adrenal cortex and homeostasis. Physiol. Rev. 30: 241–320, 1950.
254. Schally, A. V., Carter, H. W., Hearn, I. C. and Bowers, C. J.: Determination of CRF activity in rats treated with monase, dexamethasone and morphine. Amer. J. Physiol. 209: 1169–1174, 1965.
255. Schaumkell, K. W.: Über die Morphokinese und das Strukturbild der Rattenschilddrüse nach Gaben von N-(3'-dimethylamino)-propyl-3-chlorphenothiazin (Megaphen Bayer) unter verschiedenen experimentellen Bedingungen. Naunyn-Schmiedeberg's Arch. Exp. Pathol. Pharmak. 225: 381–401, 1955.
256. Schaumkell, K. W.: Über die Morphokinese der Ratten-Nebennierenrinde unter Einwirkung von N-(3-Dimethylamino)-Propyl-3-Chlorophenotiazin (Megaphen Bayer). Acta Endocrinol. (Copenh.) 20: 371–378, 1955.
257. Scott, G. T.: Melanophore dispersing action of ataraxic drugs. Biol. Bull. Mat. Biol. Lab., Woods Hole 117: 400 1959.
258. Scott, G. T. and Nading, L. K.: Relative effectiveness of phenothiazine tranquilizing drugs causing release of melanocyte stimulating hormone (MSH). Proc. Soc. Exp. Biol. Med. 106: 88–90, 1961.
259. Setekleiv, J., Skaug, O. E. and Kaada, B. R.: Increase of plasma 17-hydroxycorticosteroids by cerebral cortical and amygdaloid stimulation in the cat. J. Endocrinol. 22: 119–127, 1961.
260. Sevy, R. W., Ohler, E. A. and Weiner, A.: Effect of chlorpromazine on stress-induced adrenal ascorbic acid depletion. Endocrinology 61: 45–51, 1957.
261. Sheehan, H. L. and Summers, V. K.: The syndrome of hypopituitarism. Quart. J. Med. 18: 319–362, 1949.
262. Shibusawa, K., Saito, S., Fukuda, M., Kawai, T., Yamada, H. and Tomizawa, K.: Inhibition of the hypothalamo-neurohypophyseal neurosecretion by chlorpromazine. Endocrinol. Jap. 2: 189–194, 1955.
263. Shuster, L. and Hannam, R. V.: The indirect inhibition of protein synthesis *in vivo* by chlorpromazine. J. Biol. Chem. 239: 3401–3406, 1964.
264. Sjöstrand, S. E., Cassano, G. B. and Hansson, E.: The distribution of S^{35}-chlorpromazine in mice studied by whole body autoradiography. Arch. Int. Pharmacodyn. Thérap. 156: 34–47, 1965.
265. Sloane, R. B., Saffran, M. and Cleghorn, R. A.: Steroid response to ACTH and the effect of ataractic drugs. In: Psychoendocrinology, ed. by M. Reiss, pp. 198–204, Grune and Stratton, New York, 1958.
266. Slusher, M. A. and Hyde, J. E.: Alteration of adrenal effluent corticoid levels following forebrain stimulation in cats. Abstracts Forty-Third Meeting The Endocrine Society 100, 1961.
267. Smelik, P. G.: ACTH secretion after monoamine depletion in the hypothalamus of the rat. J. Endocrinol. 37: XV, 1967.
268. Smith, R. L., Maickel, R. P. and Brodie, B. B.: Adrenocorticotrophin (ACTH) hypersecretion induced by phenothiazine tranquilizers. J. Pharmacol. Exp. Therap. 139: 185–190, 1963.
269. Spurr, G. B., Horvath, S. M. and Farrand, E. A.: Cardiovascular effects of chlorpromazine in the dog. Amer. J. Physiol. 186: 525–528, 1956.
270. Steinberg, H. and Watson, R. H. J.: Chlorpromazine inhibition of reactions of rats to unfamiliar surroundings. J. Physiol. (London) 147: 20P–22P, 1959.
271. Sulman, F. G.: The mechanism of the "Push and Pull" principle. Arch. Int. Pharmacodyn. Thérap. 118: 298–307, 1959.
272. Sulman, F. G. and Winnik, H. Z.: Hormonal effects of chlorpromazine. Lancet I: 161–162, 1956.
273. Supek, Z., Kečkeš, S. and Voivodić, S.: The action of chlorpromazine on water and chloride excretion in rats. Arch. Int. Pharmacodyn. Thérap. 123: 253–259, 1960a.
274. Supek, Z., Kečkeš, S. and Voivodić, S.: The influence of chlorpromazine on the antidiuretic and chloruretic effects of nicotine and posterior pituitary extract. Arch. Int. Pharmacodyn. Thérap. 123: 260–263, 1960.
275. Suzuki, M., Kamio, K., Yasuda, M., Akiyama, S., Mitani, K., Oyama, T., Sato, K. and Yamashita, T.: Effect of chlorpromazine on the function of the endocrine organs. Endocrinol. Jap. 3: 67–72, 1956.
276. Suzuki, T., Romanoff, E. B., Koella, W. P. and Levi, C. K.: Effect of diencephalic stimuli on 17-hydroxycorticosteroid secretion in unanesthetized dogs. Amer. J. Physiol. 198: 1312–1314, 1960.
277. Swingle, W. W., Fedor, E. J., Barlow, G., Jr., Collins, E. J. and Perlmutt, J.: Induction of pseudopregnancy in rat following adrenal removal. Amer. J. Physiol. 167: 593–598, 1951.
278. Talwalker, P. K., Meites, J., Nicoll, C. S. and Hopkins, T. F.: Effects of chlorpromazine on mammary glands of rats. Amer. J. Physiol. 199: 1073–1076, 1960.
279. Theobald, W. und Domenjoz, R.: Zur Potenzierung narkotischer Wirkungen. Arzneimittel-Forsch. 9: 285–286, 1959.
280. Tiwari N. M., Jindal, M. N. and Jaiswal, C. L.: Effect of tranquilizing agents on water and saline induced diuresis in rats. Arch. Int. Pharmacodyn. Thérap. 128: 383–390, 1960.
281. Tokizane, T., Kawakami, M. and Gellhorn, E.: Pharmacological investigations on the antagonism between the activating and recruiting systems. Arch. Int. Pharmacodyn. Thérap. 113: 217–232, 1957.
282. Tullner, W. and Hertz, R.: Suppression of corticosteroid production in the dog by monase. Proc. Soc. Exp. Biol. Med. 116: 837–840, 1964.
283. Vandewater, S. L. and Gordon, R. A.: Largactil in anaesthesia. Can. Anaesth. Soc. J. 2: 23–31, 1955.
284. Velardo, J. T.: Induction of pseudopregnancy in adult rats with trilafon, a highly potent tranquilizer of low toxicity. Fertil. Steril. 9: 60–66, 1958.
285. Verney, E. B.: The antidiuretic hormone and the factors which determine its release. Proc. Roy. Soc., Series B 135: 27–106, 1947.

286. VERNIKOS-DANELLIS, J.: Effect of acute stress on the pituitary gland: changes in blood and pituitary ACTH concentrations. Endocrinology 72: 574–581, 1963.
287. VOGEL, G. UND TERVOOREN, U.: Über die Beeinflusung des Thyroxineffectes durch einige Neuroplegica. Med. Exp. (Basel) 4: 59–65, 1961.
288. VOGT, M.: Adrenaline and noradrenaline in nervous tissue. In: Proceedings of the Fourth International Congress of Biochemistry, ed. by F. Brucke, pp. 279–283, Pergamon Press, New York, 1958.
289. VOGT, M.: The effect of chlorpromazine and reserpine on the release of ACTH. Proceedings Second International Congress of Endocrinology, International Congress Series, Exc. Med. Found., No. 83, 635–639, 1964.
290. VOGT, M.: Effects of drugs on metabolism of catecholamines in the brain. Brit. Med. Bull. 21: 57–61, 1965.
291. WALKER, J. M.: Release of vasopressin and oxytocin in response to drugs. In: The Neurohypophysis, ed. by H. Heller, pp. 221–228, Butterworth's Scientific Publications, London, 1957.
292. WASE, A. W., CHRISTENSEN, J. AND POLLY, E.: The accumulation of S^{35}-chlorpromazine in brain. Arch. Neurol. Psychiat. (Chicago) 75: 54–56, 1956.
293. DE WIED, D. AND JINKS, R.: Effect of chlorpromazine on antidiuretic response to noxious stimuli. Proc. Soc. Exp. Biol. Med. 99: 44–45, 1958.
294. DE WIED, D., LAMMERS, J. G. R. AND SMELIK, P. G.: Pituitary adrenal activation by chlorpromazine. Abstracts of papers presented at 23rd International Congress of Physiological Sciences, Tokyo, No. 576, 1965.
295. DE WIED, D. AND MIRSKY, I. A.: The action of Δ' hydrocorticone on the antidiuretic and adrenocorticotropic responses to noxious stimuli. Endocrinology 64: 955–966, 1959.
296. WHITELAW, M. J.: Delay in ovulation and menstruation induced by chlorpromazine. J. Clin. Endocrinol. 16 972, 1956.
297. WHITTEN, W. K.: Endocrine studies on delayed implantation in lactating mice. J. Endocrinol. 16: 435–440, 1958.
298. WINNIK, M. H. Z. ET TENNENBAUM, L.: Apparition de galactorrhée au cours du traitement de largactil. Presse Méd. 63: 1092, 1955.
299. WIEMAN, R. JR.: The effect of acute and chronic administration of chlorpromazine on the I^{131} distribution in normal rats. J. Pharmacol. Exp. Therap. 138: 269–276, 1962.
300. WRIGHT, E.: Use of chlorpromazine in the measurement of radioactive iodine in the thyroid gland of the rat. New Zeal. J. Agr. Res. 1: 455–461, 1958.
301. YOKOYAMA, A. AND SAWYER, C. H.: Effects of reserpine and chlorpromazine on the milk ejection reflex in lactating rats. Proc. Soc. Exp. Biol. Med. 121: 370–373, 1966.
302. ZARROW, M. X. AND BROWN-GRANT, K.: Inhibition of ovulation in the gonadotrophin-treated immature rat by chlorpromazine. J. Endocrinol. 30: 87–95, 1964.
303. ZIMBARDO, P. G. AND BARRY, H.: Effects of caffeine and chlorpromazine on the sexual behavior of male rats. Science (N.Y.) 127: 84–85, 1958.
304. CRANSTON, E. M.: Antiestrus drugs on subestrus of ovariectomized C_3H mice. Proc. Soc. Exp. Biol. Med. 108: 514–518, 1961.
305. DEWS, P. B. AND MORSE, W. H.: Behavioral pharmacology. Annu. Rev. Pharmacol. 1: 145–174, 1961.
306. GOLLUB, L. R. AND BRADY, J. V.: Behavioral pharmacology. Annu. Rev. Pharmacol. 5: 235–262, 1965.

ERRATUM

In the review by F. Buffoni of Histaminase and Related Amine Oxidases, vol. 18, p. 1170, table 2, i, "cyclic" ought to be "sulfur".