promazine and chlorprothixene were the same as those which caused ataxia.

A suggestion is offered according to which the ratio of effective doses of a compound in different tests may be indicative of its therapeutic effectiveness. Recently, Freed (1960) reported a clinical investigation of amitriptyline which showed its antidepressant properties in depressed patients.

80 Differentiation of Central Depressants by Means of the Veratramine Excitation. W. SCHOETENSACK and G. HALLMANN (Germany).

Veratramine in small doses evokes tremors, in higher subletal doses convulsive-like excitation phenomena.

Studies in rats and mice have shown the following results: (1) Tremor and convulsions are only suppressed by a few centrally acting muscle relaxants such as mephenesin, zoxazolamine, 2-aminobenzthiazole, chlormezanone and carisoprodol, whereas meprobamate and 2-(γ-methoxypropylaminomethyl)-1:4-benzodioxane-HCl fail to block the veratramine excitation; (2) A number of unsaturated tertiary alcohols, urethane, chloral hydrate and phenylacetylurea abolish the veratramine convulsions but not the tremor.

Hypnotics and anticonvulsants such as phenobarbital, hexobarbital, phenytoin, and troxidone, also a number of tranquillizers, ganglionic blocking-, sympathicolytic-, and anticholinergic agents are ineffective against tremor and convulsions up to the level of lethal doses.

The two excitation phenomena induced by veratramine differ completely in their unusual resistance against most of the investigated drugs from the excitations produced by leptazol, strychnine or by harmine and tremorine.

Transections of brain in rat suggest that structures within the lower brain stem are responsible for initiating the veratramine excitation.

Transections in the higher brain levels including the diencephalon do not change fundamentally the reactions after application of veratramine. After removal of the cerebellum convulsions appear but not tremor.

Decerebrate rigidity in rat is intensified by the central excitants mentioned above, including harmine and tremorine; veratramine, however, completely prevents the hyperactivity of the extensors and after cessation of the veratramine excitation the decerebrate rigidity appears unchanged.

Since the veratramine excitation is completely inhibited only by a limited number of centrally-acting muscle relaxants, these findings seem to be of considerably value for evaluation and differentiation of central muscle relaxants.

The nervous mechanisms probably responsible for the initiation and evidently specific inhibition of the two stages of the veratramine excitation are discussed.

81 Three Types of Artificially Induced Tremors and the Effect of Some Antiparkinsonian Agents upon Them. I. L. BONTA and H. M. GREVEN (Holland).

Usually antiparkinsonian drugs are pharmacologically evaluated by testing them against varying types of tremors produced by surgical methods (tremor-monkey) or chemical means (nicotine, Tremorine). In the course of our investigation of the effect of intracerebral drug injections, we observed that a new compound, Gre-1248, induced a type of hyperkinesia (running fits and hind-limb tremor), which reminded us of certain motor disturbances occurring in extrapyramidal syndromes. The effect of nicotine, Tremorine and Gre-1248 on mice will be demonstrated by a short film.

Antagonistical studies with several antiparkinsonian drugs (atropine, caramiphen, trihexyphenidyl, orphenadrine, diethazine, etc.) have shown that the various compounds induced different degrees of protection against the three types of tremors. The question of parallelism between experimentally-induced tremors and Parkinson's disease or related extrapyramidal disorders will be briefly discussed.

82 A Contribution to the Pharmacology of Tremorine-induced Tremor. P. STERN and J. GAŠPAROVIC (Yugoslavia).

The onset of tremorine-induced tremor (TT) in mice is delayed by application of iproniazid or PIH 20 hr prior to tremorine (T); similarly applied hydralazine or α-methyl DOPA have the opposite effect. Since iproniazid and PIH increase dopamine, serotonin (S) and GABA in the CNS, the three precursors, DOPA, 5-hydroxytryptophan (5-HTP) and glutamic acid were examined. Only 5-HTP delayed TT and harmine-induced tremor, but not that induced by 3-amino-1:1:3-triphenylpropan-1-ol or diethylcysteamine. DOPA and glutamic acid did not act on either kind of tremor. When T was preceded by iproniazid (20 hr) and 5-HTP (2 hr) TT was delayed considerably further than by action of either substance alone. Consequently, an increase of S in the CNS delays TT, although T itself has no influence upon the S-level. The fact that hydralazine and α-methyl DOPA, two inhibitors of amino-acid decarboxylases, are capable of inducing tremor, favours this assumption. S-antagonists, harmine and LSD also induce tremors. Reserpine and chloropromazine-induced Parkinsonism is interpreted on the basis of these facts. In contrast to chloropromazine, reserpine reduces the level of dopamine, the concentration of which is particularly high in the corpus striatum. The latter contains, in addition, much S, substance P and choline acetylase. We have found that S potentiates this enzyme, but so does T alone. It is open to discussion whether accumulation of S in definite regions, e.g. the corpus striatum, can lead to an inhibition of TT. The present results pre-

clude the possibility of dopamine being the responsible factor.

83 The Blood–Brain Barrier. H. DAVSON (United Kingdom).

The various factors determining the rate of penetration of substances from blood to the nervous tissue of the brain and spinal cord will be discussed.

84 Exchange between Cerebrospinal Fluid and Blood. J. R. PAPPENHEIMER and S. R. HEISEY (U.S.A.).

Large bore cannulae have been implanted over the cerebral ventricles and in the cisternae magnae of goats. Animals survive in good health and their ventriculo-cisternal systems may be perfused with synthetic CSF of normal ionic composition without detectable circulatory, respiratory or behavioural changes. Steady-state transfer rates between CSF and blood can be measured from differences between inflow and outflow of test substances. Normal permeabilities (flux rates per unit concentration difference) to creatinine and inulin average 0·19 and 0·12 ml/min, respectively, and may be accounted for by passive processes. Diodrast and phenol red (in low concentrations) are removed rapidly from CSF to blood by a process of active transport resembling secretion by the proximal tubules of the kidney; clearances of these substances from CSF may exceed 1 ml/min. The locus of active transport occupies a volume of about 2 ml in the region of the fourth ventricle and cistern magna.[1] The extraction of K^+ from CSF perfusion decreases with increasing concentration, suggesting that this ion is also removed by active transport. Preliminary experiments indicate that large increases of K^+ are required to produce a rise in blood pressure comparable with that caused by a small decrease in Ca^{++}. It is possible that an active transport system for K^+ must be saturated before an increased concentration in CSF can penetrate to fluid immediately surrounding neurones.

1. (1960), *Amer. J. Physio.*, **200**, 1.

85 Discussion of Previous Paper. D. P. RALL (U.S.A.).

86 Pharmacology of Aqueous Humour Formation and Outflow. E. BÁRÁNY (Sweden).

Some anatomical and physiological facts concerning the ciliary epithelium and the trabecular meshwork in the angle of the anterior chamber will be briefly presented. The methods used for the measurement of rate of production of aqueous humour and its outflow resistance will then be critically surveyed. Finally, what little is known concerning the pharmacology of the secretory system and the outflow system will be discussed.

87 Discussion of Previous Paper. T. MAREN (U.S.A.).

88 Pharmacological Control of Prolactin Secretion and Lactation. J. MEITES (U.S.A.).

Many substances can induce prolactin release from the anterior pituitary of rats and/or rabbits, and elicit mammary growth and secretion. These include oestrogens, progesterone, testosterone, cortisol, adrenalin, noradrenalin, acetylcholine, serotonin. pilocarpine, eserine, atropine, amphetamine, morphine, reserpine, chlorpromazine, meprobamate and several carcinogens; rat hypothalamic extract and Guillemin's CRF; electrical stimulation of the head, nasal mucosa, nipples, lumbar region and uterine cervix; non-specific stresses such as cold, heat, restraint or formalin injections; and transplantation of the rat pituitary to the kidney capsule. Large doses of oxytocin, vasopressin, histamine, Dibenemine and LSD 25 were unable to elicit mammary secretion.

The effective agents apparently released ACTH as well as prolactin, since both hormones are necessary to elicit mammary secretion in intact rats, and thymus wt. was significantly reduced. These agents were ineffective in hypophysectomized rats. Induction of mammary secretion by pituitary transplantation confirms the view that the CNS normally inhibits prolactin release; however, it is doubtful that all agents used inhibited the CNS, i.e. rat hypothalamic extract, Guillemin's CRF and some drugs. Also, in hypophysectomized rats with pituitary transplants, injections of reserpine, serotonin, adrenalin, acetylcholine or formalin significantly increased the percentage of rats showing mammary growth and secretion. Some agents may therefore stimulate a CNS centre(s) which activates the anterior pituitary to induce mammary growth and secretion. Cultures of pituitary explants *in vitro* secrete substantial amounts of prolactin[1] and studies are now in progress to determine which agents can directly influence this process.

1. MEITES, KAHN and NICOLL (1961). Programme of 43rd Meeting, The Endocrine Society, page 3, June 22–24, New York, N.Y.

89 Control of Ovulation in Women. G. PINCUS and C.-R. GARCIA (U.S.A.).

In women suggestive, but not conclusive evidence of the suppressive action of progestins has been noted by means of the indices of ovulation (basal body temperature, vaginal smears, endometrial biopsies and urinary pregnanediol). Of these, marked reduction of urinary pregnanediol excretion is indeed most suggestive. Furthermore, inspection of the ovaries at time of laparotomy during the latter phases of cyclic administration of progestins also confirms the failure of ovum release. Although inconsistent results as regards reduction of total